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DETACHMENT OF THE RETINA

Pathologic and Therapeutic Considerations

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GONIN'S demonstration that retinal detachment is cured by sealing the retinal tears clarified and oriented the previously vague conceptions of the etiology, pathogenesis and therapy of this process. Fundamental concepts have been accepted as basic, even though some of these concepts have been modified during the past fifteen years as a result of the examination of a large number of patients with much greater care than was observed before the time of Gonin. All are aware that studies of the fundus used to involve the posterior pole of the eyeball with much less attention on the details of the periphery of the retina than is now given. Few oculists knew that tears are present in the great majority of cases; and in some cases of detachment the lesion was diagnosed as some other condition.

Detailed studies of the ocular fundus and histologic examinations of enucleated eyeballs have demonstrated that in cases of idiopathic detachment the retina is much altered. Indeed, it is strange that retinal detachment is not of more frequent occurrence. Some eyes which have a congenital predisposition to detachment reveal ophthalmoscopic evidence of atrophy and cystoid degeneration. In histologic studies, atrophic and degenerative lesions are seen to reduce the thickness of the retina to one-third normal, at times over large areas. Thus, for each patient with a detached retina there are many others who are predisposed to the same condition. The only factor which is lacking is the adhesion of the retina to the framework of the vitreous, which elevates the retina as a result of jerks or ocular movements. Even in a certain number of these patients, many more than was at first believed, the retina does not detach even though a hole is present in this membrane for a long time. Such a condition was previously considered a rarity, but if the retinas are examined with great care it is encountered more

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frequently. During the past eighteen years of my professional practice I have observed more than 40 cases of retinal holes without detachment.

PATHOLOGIC CONSIDERATIONS

In order that the retina may detach, the margins of the tear must invert slightly toward the interior of the eye, so that with movements of the eyeball the vitreous strikes against them. This destroys the framework of the vitreous, which passes behind the retina. The elevation of the margins of the retinal hole is facilitated by postinflammatory, degenerative or senile retraction of the framework of the vitreous.

It is known that the retina does not detach if it is adherent to the choroid as well as to the framework of the vitreous. For this reason, chronic and degenerative processes are more likely to predispose to retinal detachment than are intense chorioretinal inflammatory processes. Certain acute lesions, such as retinal periphlebitis, exudative choroiditis, von Hippel-Lagleyze disease and albuminuric retinitis, are exceptions. With such lesions rents are usually not present, but when they occur they indicate a previous adhesion between retina and choroid, not between vitreous and retina. Macular holes come into this category.

Trauma.—Trauma as the determinate cause of retinal detachment does not have the important role which has been conceded to it in the past. In the first place, retinas do not detach unless they are diseased, except after extensive traumatism; secondly, many times there is no real antecedent trauma; and, lastly, ocular trauma is relatively infrequent as a cause of detachment. More frequent causes are a blow on the cranium, a fall on the heels, sneezing, coughing and, above all, excessive stooping. This last mechanism is very frequent as a cause of detachment, especially in patients who have been operated on for cataract. It concerns persons who stoop to remove or put on footwear; or persons who have been in a stooping position for some time while gardening, whether watering, digging or weeding; or persons who are obliged to stoop frequently in their work, or who occasionally pick up objects from the floor, etc.

It is therefore advisable to warn persons who are predisposed to detachment of the retina (patients who have had a cataract operation, especially those who were myopic) to avoid stooping, to place the foot on a chair when putting on the shoes, to use a long-handled tool in gardening, to kneel down in picking up an object from the ground, etc.

Pathogenesis.—The fundamental concept of the movements of the eyes as the factor which initiates and increases the detachment is becoming more definite, but the distinct clinical types of the disease and, above all, the varieties of its evolution show that other factors are also important.

Actually, all have seen cases of recent detachment with extensive bulging which flattens into place in one or two days of rest in bed and bandaging. In other cases of equally fresh detachment with but little bulging of the detached retina, there is little, if any, improvement with repose. One known factor of influence in these cases is the size of the retinal rent. When the tear is small, there is rapid resorption of the subretinal fluid; when the hole is large, resorption is slow. With the cases of extensive tears belong those with disinsertions, which improve little, or not at all, with repose, even though the hole may not be large.

The rapidity with which the retina tears is of great prognostic value. If the holes are small and do not enlarge, there is evidence that the adhesions between vitreous and retina are not large, and the prognosis is good. On the other hand, the rapid formation of large tears indicates extreme friability of the retina or the existence of extensive adhesions between retina and vitreous, rendering treatment ineffective.

THERAPEUTIC CONSIDERATIONS

The factor of time, which used to be considered of such importance and which enhanced the urgency of operation, is being disregarded. Given equal conditions of extent and bulging of the retina, it is much easier to cure a detachment of one or two months' duration with a small rent than one only a few days old with a large tear. The urgency in most cases does not lie in surgical intervention so much as in the need for bandaging the patient's eyes and enforcing relative repose.

Another of the factors which has most influence on the evolution of the retinal detachment and on its cure is the condition of the choroid. During the last few years I have attached considerable importance to this factor. Just as the retina becomes detached because it is altered, so the choroid must be assumed to be changed, in view of the effect which pathologic processes of the one have on the other. However, it has been seen that intense processes do not predispose to detachment because adhesions are created between the two structures. Therefore, not much change in the choroid is required to make a retinal detachment possible. In many cases the ophthalmologist is not aware of the degree of change, and he can enlighten himself about this only by the condition of the fundus and the clinical course of the detachment. A detachment which is replaced with rest has a good prognosis, for the choroid is demonstrated to be in good condition for reabsorption. This proves its relative integrity, a necessary condition for exudation under irritating thermic action and for later reabsorption of the exudate and of the remaining subretinal fluid.

On the other hand, there are cases of recent detachment in which an apparently benign ophthalmoscopic picture is present (small hole and little retinal prominence) but in which there is little, if any, improvement with rest and a severe reaction on surgical intervention occurs.

These cases, which differ from the preceding type, are those in which the choroid has no capacity to reabsorb and in which its probable inflammatory state causes it to respond to surgical attack with a severe local reaction. A similar reaction also appears in the episclera and in the bulbar conjunctiva.

Owing to this variable reactivity of the choroid, which cannot always be predicted, the prognosis of retinal detachment can be only approximate. In some apparently simple cases treatment fails, while in others with extensively detached retinas the outcome is successful because the choroid is healthy and has great absorptive powers.

Likewise, the manner in which the choroid reacts has an influence on the intraocular pressure, aside from the part which the ciliary body itself plays. Some years ago it was believed that very low intraocular pressure was of bad prognostic significance and that normal pressure was a favorable sign. In general, this principle can be accepted, but with many reservations.

If there are large recent tears, the tension is usually low. However much the choroid absorbs, it is not able to absorb all the vitreous which passes behind the retina. After a few months, even though the large rents persist, the tension rises to normal because the choroid cannot absorb more and is undergoing atrophy.

If the holes are small and the tension is reduced, the prognosis is often good, because this indicates choroidal absorption of the subretinal fluid. If the holes are small and the intraocular pressure at the same time remains elevated, the prognosis may be less favorable than would otherwise seem apparent, since this may indicate poor absorptive ability of the choroid.

As already indicated, irritation of the ciliary body may alter these relations, since it is clinical experience that cyclitis may be accompanied with elevated or reduced intraocular pressure.

It is an undoubted fact that the vitreous acts as a foreign body on the choroid, which is finally destroyed. For this reason, all retinal detachments of more than two years' duration are accompanied with complete atrophy of the choroid, as revealed by ophthalmoscopic examination and histologic study. To produce this atrophy, it is logical to assume that the vitreous has acted as an irritant to the choroid. The manner in which the choroid reacts in each case probably varies in different patients; this may be a partial explanation of the various forms of clinical evolution of retinal detachments. To this variable choroidal response to contact with vitreous is added the variable reaction to surgical thermic intervention. Therefore, in the immediate postoperative period, if the eye is not hyperemic, the pupil dilates well and the patient has no pain, the prognosis is much more favorable than if the patient is in pain, the pupil does not dilate with atropine and the eye is hyperemic—all of which are symptoms of uveitis.

Consequently one is forced to the conclusion, already stated so often in part by other authors and by myself, that it is advisable to localize the diathermic action as much as possible. To attain this, a thorough study of the fundus is necessary. To be sure, it is easier and more convenient not to make a detailed study of the fundus by means of direct and indirect ophthalmoscopy, substituting for this procedure lavish use of diathermy over an extensive area. But this convenience is prejudicial to the patient by reducing the chances of a successful result. If it becomes necessary to reoperate, the difficulties are considerably increased in an eye which has undergone excessive diathermic treatment.

Immediate repetition of the operation is advisable only when tears appear which were not reached by the preceding diathermic action. If a second operation is thus indicated, efforts should be made to insure that at least twenty days have elapsed since the first operation, that the eye does not suffer from the pain and photophobia which are characteristic of iridocyclitis and that an exaggerated local reaction is not present. In the cases in which recurrence takes place within the first two months after operation, if no tears are seen or if those which appear are situated in the area treated by diathermy, it is best not to reoperate. It is preferable to apply a binocular bandage and to make the patient rest in bed. The result of the operation may yet be successful. In certain cases with a large bullous retinal pouch, puncture of the site and injection of air into the vitreous may contribute to a cure.

Treatment of retinal detachment gives the highest percentage of successful results if it is based on the following management:

1. Thorough exploration of the entire retina by direct and indirect ophthalmoscopy, using a strong illumination with the pupil dilated maximally.

2. Repose of the patient with binocular bandage in bed, or almost horizontally in an easychair, before operation if the retina which surrounds the tear is close to the choroid. If the condition of the eye does not improve after fifteen or twenty days, operation may be undertaken, even though the prognosis is guarded. Although there are cases in which more time is required for the retina to become reattached, it is dangerous to wait longer, because macular vision will be more involved, especially in detachments involving the superior temporal quadrant. It is known that retinal separation in the inferior nasal quadrant is less serious with respect to macular vision and deteriorates more slowly.

3. Use of as limited diathermic action as possible, based on accurate localization of the tears, coagulation with weak intensity and as little fulguration as possible. Fulguration burns and irritates the tissues and causes the formation of toxic products, which are irritating to the choroid and prejudicial to a cure. There are patients who do well in spite of the inadeptness of the surgeon, but the percentage of successes is low under such conditions.

4. Ophthalmoscopic control during the operation, transparency of the cornea being maintained by instillation of a very little local anesthetic and by continuous moistening with saline solution. If a retinal bulla is present, it should be punctured with a very fine diathermic needle after surface diathermy of the area under the most sloping part and after injection of sterile air at the level of insertion of one of the rectus muscles in an amount to correspond with the size of the retinal prominence. It is a good sign if the subretinal fluid flows out and then suddenly stops, indicating that the retina or the thick vitreous is thus plugging the hole. The eye then regains its tension, and at the same time the cornea becomes opaque. Sometimes 3 cc., or even 4 cc., of air must be injected.

5. Ocular and general postoperative repose. This must be as complete as possible during the first weeks after operation, with the patient supine in most cases and semisupine in cases of inferior disinsertions and of elderly persons. The position of the head is thought not to be as important as was formerly believed, since in cases in which the patient for one reason or another could not lie on the side of the retinal holes a successful cure was as easily obtained. Perhaps, since the subretinal fluid is denser than the vitreous (as demonstrated by Weve in 1933 and confirmed by others), the position on the side opposite the tears helps the fluid to slip toward the area of intact retina, where healthy choroid can absorb it. This is a hypothesis which only further experience can confirm. In any case, one can be guided by the appearance of photopsias and place the patient on the side in which they are least evident. If photopsia is not present, so much the better, since it is evidence that the retina does not oscillate. The period of almost absolute ocular and general repose varies between ten and thirty days in bed followed by thirty to one hundred days of semirepose, the period depending on the severity of the condition.

6. General tonic treatment of the patient. The presence of general and accompanying focal causes of the ocular lesion should be looked for, but one should lose no time in investigations without keeping the patient at rest with his eyes bandaged.

7. If a relapse takes place during the first weeks, especially when the patient arises from the bed, complete ocular and general repose is resumed unless new holes or preexisting tears which were overlooked are seen outside the zone treated with diathermy. An attempt should be made to limit the diathermic action.

The removal of the patient to his home presents a problem if he lives at a great distance. In good weather transport by airplane is the best method. When this means is not possible, the patient may be carried home by automobile or train; he must not lie in bed or support his shoulders and back on the back of the seat; but his position must be such that his trunk may act as a shock absorber for his head.

FLUORESCENT COLORS IN TANGENT SCREEN EXAMINATIONS

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THE NUMEROUS devices for the taking of perimetric fields indicate that manufacturers are always endeavoring to devise a machine which will least divert the patient and thus enlist his cooperation in this subjective test.

Perimeters are usually constructed so that the isopter recordings are out of view of the patient, usually at the back of the instrument. This is a distinct advantage so far as the results obtained are concerned. On the other hand, the ophthalmologist does not get the complete picture until the entire field is plotted.

When the tangent screen is used, the recording is clearly seen on the board, and the observer can note very early in the examination at which portion within the 30 degree area there is evidence of scotoma or sector defect. The ophthalmologist can then carefully analyze this location without fatigue to the patient. In the examination of patients with the tangent screen, notations are made by a variety of colored pins or chalks. This array of colors tends to increase the subject's curiosity, and one notes occasional movements of the eye from the point of fixation.

With the colored pins, it is somewhat difficult to take the fields of both eyes at one time. Usually one field is taken; the readings are transferred to the record sheet; the pins are removed, and the procedure is repeated for the other eye. Some tangent screens are made of cloth, so that the pins are easily inserted. The screen is then reversed for the taking of the field of the other eye. This is somewhat less time consuming, though it also inordinately delays the examination. Furthermore, pins often tear the fabric in a cloth tangent screen. After a short period of use we note a "turning" of the free edges of the tangent screen—the inner and outer sides. (The upper and lower parts of the screen are held straight by poles running along their borders.)

From the clinic of St. Christopher's Hospital for Children.

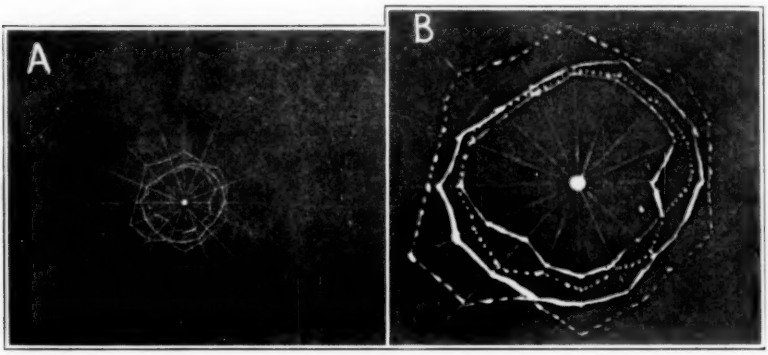
Read at a meeting of the College of Physicians, Philadelphia, Section on Ophthalmology, Feb. 21, 1946.

In view of these difficulties, it appeared to us that the speed and efficiency of this examination could be improved. The ordinary blackboard or tangent screen now in use could be utilized, but in place of the chalks and pins fluorescent water colors, which can be easily washed off, could be employed in plotting the isopters.

METHOD

The technic in taking the field does not vary in any respect from the usual one except that the recordings of the isopters are made by fluorescent colors, almost invisible in white light. These are applied with a fine, inexpensive camel's hair brush glued to an applicator. The pigments are of the water color type,[1] are not dangerous to handle and can be conveniently washed off with either water or soap and water.

The ophthalmologist can readily see the notations on the tangent screen under the usual 7 foot candle illumination used in the test.



In *A*, the screen was exposed to the light for several weeks but did not lose its quality of fluorescence. The pigment cannot be erased except with water. This photograph was taken with the aid of two Photo-Flood lamps, at a distance of 2 meters.

B is the same picture taken in absolute darkness with one small, hand type ultraviolet ray lamp. This being a black and white film, one does not see the fields in the actual colors, as portrayed on the tangent screen. This photograph was taken at a distance of 1 meter.

After the study is completed, the ultraviolet light is turned on. Within several minutes the entire field becomes clearly and brilliantly illuminated. The records are now ready for transferral to the history chart.

COMMENT

Any tangent screen now in use can be easily converted into the fluorescent type by going over the circles and meridians with fluorescent green pencil. These lines in fluorescent pencil are quite invisible to the patient. As for the ultraviolet ray lamp, almost every hospital

1. Fluorescent colors can be obtained from Stroblite Co., New York, or Switzer Brothers, Cleveland.

has one for use, in the pathologic, dermatologic or ophthalmologic department.

The fluorescent equipment is inexpensive and should last for a number of years

The figure shows photographs of the fields in a case of retinitis pigmentosa plotted on the tangent screen. *A* was taken with fluorescent colors and illuminated with ordinary light. The stimulus used was a 4.5 mm. test object at 1,000 mm. Dotted lines are used for the field of the right eye; solid lines, for the field of the left eye. The outer lines are for white stimulus the inner lines, for red stimulus. *B* is the same screen illuminated with ultraviolet light.

SUMMARY

A method is shown by which fields can be taken on the tangent screen under regular illumination and plotted with the ordinary targets now in use, but marked off by invisible fluorescent colors read under ultraviolet illumination.

37 South Twentieth Street.

USE OF BERMAN LOCATOR IN REMOVAL OF MAGNETIC INTRAOCULAR FOREIGN BODIES

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DURING the past two years, at the New York Eye and Ear Infirmary, a relatively new instrument, the Berman Locator, has been found increasingly useful for intraocular foreign body work. In fact, experience with this device has demonstrated that the best foreign body work cannot be done without it.

Among a considerable number of cases of intraocular foreign bodies encountered during that period, we have had at least 6 in which the body was at first given up as nonmagnetic because of lack of response to the giant magnetic extractor but was later shown to be magnetic by the Berman Locator and was removed. The initial failures in these cases occurred because roentgenologic localization alone was inadequate to enable the surgeon to apply the proper magnetic power at the correct site to get a response.

In 1 case different surgeons made three attempts to remove the foreign body without getting the slightest response with the giant magnet and concluded that the foreign body was nonmagnetic. Nine months later the Berman Locator, which had not before been available, showed that the foreign body was magnetic, and it was readily localized. However, it was too late to save the eye, for degeneration had already set in. A chart showing two roentgenographic localizations of the foreign body is presented (fig. 1), with a photograph of a section of the eye (fig. 2). It will be seen that the roentgenograms differed and were thus a source of confusion. The inability to get a response to the giant and hand magnets was obviously due to failure to apply the magnets in the correct location.

These experiences raise the question: "What is the Locator and what has it to offer the ophthalmologist that the x-ray machine does not have?" Briefly, the Berman Locator is a portable electromagnetic device similar in size and appearance to a radio, for the detection and localization of metallic foreign bodies, in particular the magnetic metals (iron and steel). It came into prominence in December 1941, when, during the attack on Pearl Harbor by the Japanese, Dr. John J. Moorhead, of New York—for whom the Locator was originally designed by Mr. Samuel Berman, an engineer—demonstrated in the treatment of

casualties of that attack the speed and accuracy with which the Locator would detect and localize magnetic foreign bodies.

The Locator gives the surgeon the following practical aids not available to him heretofore:

First, and foremost, it is a localizer that he can use himself, if necessary, at any time, in any place and in any emergency.

The Locator is self sufficient in many cases for all preoperative and operative localization of magnetic foreign bodies; and when roentgenograms and expert ocular roentgenographic localization are not readily available, the Locator becomes indispensable to the ophthalmic surgeon, for an intraocular foreign body is always an emergency.

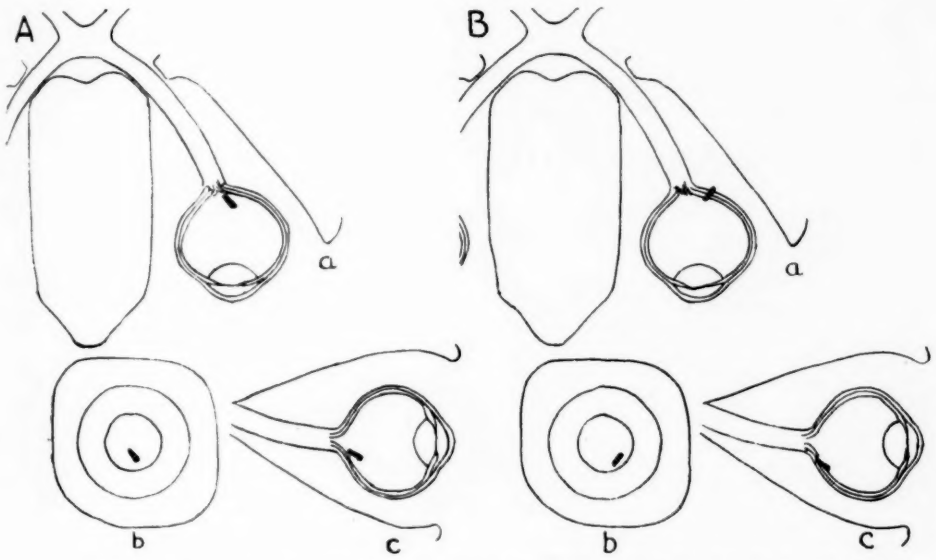

Fig. 1.—Two roentgenographic localizations of the same foreign body (1 by 1.5 by 2.5 mm.) in the left eye; scale full size.

The data on the position of the foreign body are as follows:

(*A*) Back of center of cornea: anterior end, 19.5 mm.; posterior end, 21.5 mm. Horizontal plane: anterior end, 3 mm. below; posterior end, 2 mm. below. Vertical plane: anterior end, 0.5 mm. to temporal side; posterior end, 1 mm. to nasal side.

(*B*) Back of center of cornea: anterior end, 21.5 mm.; posterior end, 24 mm. Horizontal plane: anterior end, 4.5 mm. below; posterior end, 2.5 mm. below. Vertical plane: anterior end, 1.5 mm. to temporal side; posterior end, 3 mm. to temporal side.

In both *A* and *B*, *a* represents a horizontal section; *b*, a front view, and *c*, a side view, of the eye.

In the operating room, the Locator provides localization of pinpoint accuracy with which to check and, if necessary, to correct the roentgenologic localization previously obtained. If the position of

the foreign body changes, owing to gravity or surgical manipulation, this knowledge is made available instantly.

Since intraocular foreign bodies are usually removed by magnetic extraction, it is important to know beforehand whether, and to what degree, the foreign body is magnetic, in order that the proper degree of magnetic force may be used for the extraction. The Locator provides this information, which is valuable, as too much magnetic force causes added injury to the eye and too little is ineffective.

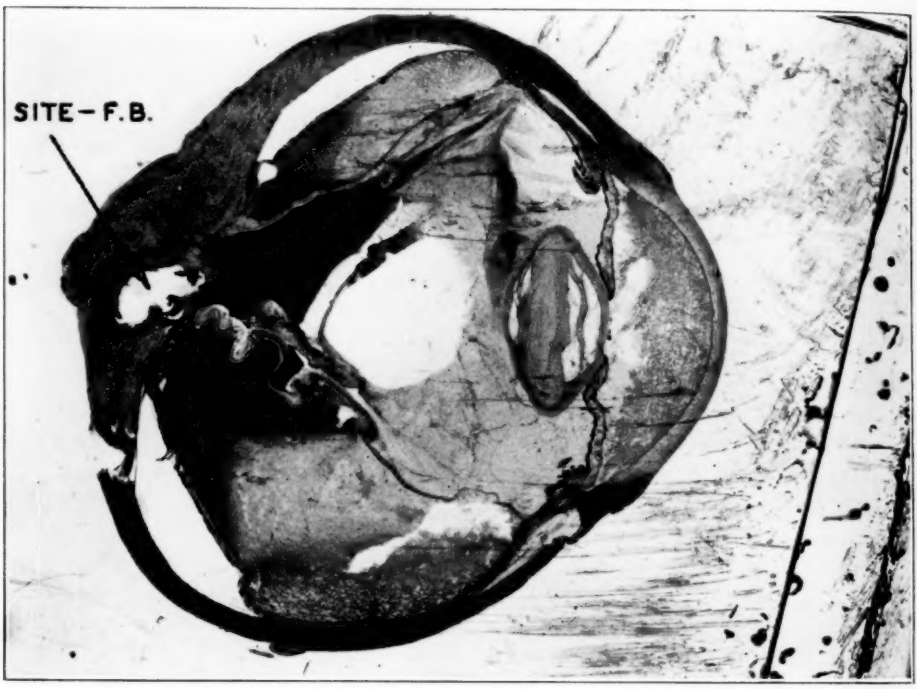

Fig. 2.—Section of eye, showing actual location of the foreign body indicated in figure 1.

The detecting element of the Locator is sufficiently small for practical use in intraocular foreign body work and is sterilizable.

At the New York Eye and Ear Infirmary we have found the operation of the Locator simple and readily mastered by the regular operating room personnel and surgical teams, who have learned to use it successfully, without difficulty.

ROENTGENOLOGIC LOCALIZATION AND THE BERMAN LOCATOR

Roentgenograms and roentgenographic localization of intraocular foreign bodies are valuable and often indispensable and, where avail-

able, should not be omitted. They show the presence of most foreign bodies, whether magnetic or not, and they furnish a permanent record that there was a foreign body. They also show its size, shape and general disposition, which constitutes essential preoperative information.

To be of value for the localization of intraocular foreign bodies, however, this type of roentgenologic work must be done by highly skilled specialists who are especially versed in the better technics of ophthalmic roentgenologic localization, such as the Sweet, Vogt or Comberg method. As many communities do not have roentgenologic special-

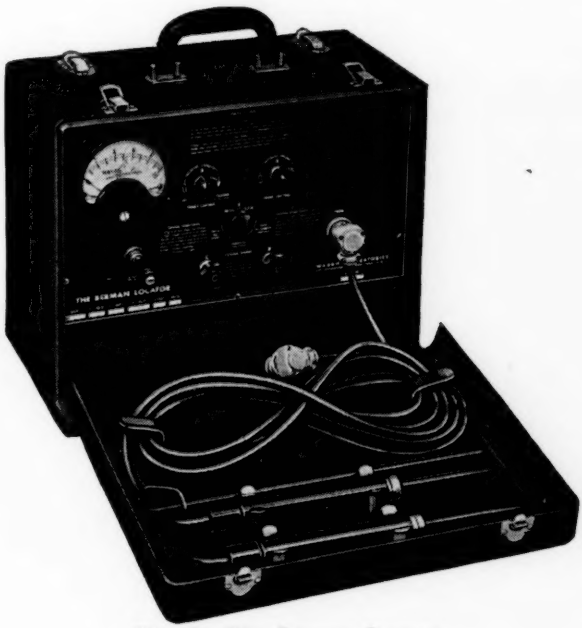

Fig. 3.—The Berman Locator.

ists of this type the electromagnetic localizer fills for them an especial need.

A small percentage of roentgenologic localizations, even by experienced persons, are at times, for one reason or another, sufficiently in error to result in failure to extract the foreign body after the patient reaches the operating room. It is a mistaken notion that an error of 1 or 2 mm. is not serious and that the extracting magnet will always cause the fragment to come "from around the corner" even when the incision is slightly removed from the true site. We have had cases at the New York Eye and Ear Infirmary in which the magnetic extractor was ineffective until a difference of 1 mm., as indicated by the

Locator, was corrected. After the incision was extended 1 mm. in the direction indicated, the foreign body came out immediately. Sometimes roentgenograms taken by the same technician and interpreted by the same specialist disagree and cause confusion. In cases such as those cited, the Locator settles the question of localization simply and directly.

Another situation that occasionally, although infrequently, faces the surgeon is a negative roentgenogram despite the existence of a small foreign body. The successful removal of such a foreign body with the aid of the Berman Locator alone was reported recently by Dr. A. R. Sherman, of Newark, N. J.[1]

The combined use of the Locator with roentgenograms meets most of the ideal requirements for localization of foreign bodies. The roentgenogram discloses the presence of the foreign body, its dimensions and general disposition. The Locator tells immediately whether it is magnetic and approximately to what degree. The instrument is then taken into the operating room to be used for checking any previous roentgenographic localizations, which it is capable of doing with absolute accuracy in the hands of the operating room team alone. As the operation proceeds and tissues are disturbed, or if the foreign body has moved, immediate reorientation of the foreign body is available without the necessity of waiting for new roentgenograms to be exposed, developed and interpreted. Localization with the Locator is simple, direct, immediate and precise.

OPERATION AND TECHNIC

The operation of the Locator and the adjustment of the controls are relatively simple; at the New York Eye and Ear Infirmary this work is done by the nursing staff. The standard instrument operates on 110 volts alternating current, but models can be built for 110 volts direct current or 6 volt battery operation.

The technic for localizing ordinary intraocular foreign bodies located within or close to the sclera is simple when complete exposure of the surface of the globe at the approximate site is possible.

This involves no more than passing the tip of the sensitive probe over the suspected area and observing the indicating meter or listening to the changing pitch of the built-in loud speaker. As the probe approaches the site of the foreign body, the meter needle rises on the scale, and simultaneously the sound from the speaker rises in pitch. The position on the surface where the peak indication is obtained marks the precise spot for incision.

1. Personal communication to the author.

After the scleral flap is lifted, the tip of the probe may again be applied over the exposed area for reorientation of the precise spot in the choroid for incision. Thus, the operation is characterized by the utmost precision throughout.

The technic is somewhat modified in cases of foreign bodies situated far posteriorly, in which complete exposure of the affected area is difficult and in which there may be a possibility that the foreign body is extraocular and is located within the tissues of the orbit, and not within the globe. While in actual practice the localization in these, more difficult, cases is as rapid as in the simpler cases, a much more intimate knowledge of and familiarity with this technic are required. Besides a study of the technic, some actual practice in the localization and extraction (with forceps) of small foreign bodies buried in a

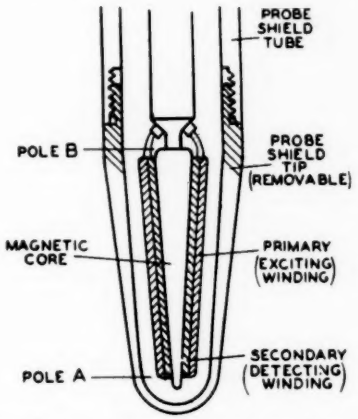

Fig. 4.—Construction of the probe of the Berman Locator.

suitable medium, such as plastic modeling clay, is essential for complete familiarity with the technic. This normally requires but a few hours and once mastered becomes very simple. To an ophthalmologist who has so many difficult technics to master, this is virtually child's play; nevertheless, the preliminary practice in clay is necessary to make sure that the principles are thoroughly understood and to acquire the degree of skill and familiarity necessary for the operating room.

A description of the principles of the Locator and their application to ophthalmology follows.

PROBE

Figure 4 is a diagrammatic section, somewhat exaggerated, of the Locator probe, showing the principal parts. The primary, or exciting winding, creates an alternating magnetic field about the probe and renders its magnetic core a bar magnet having two magnetic poles, *A* and *B*,

as shown. Through the secondary, or detecting winding, the changes in this field caused by the approach of a metallic body register on the indicator. The closer the approach of a metallic body to the probe, the higher the indication. The alternating field about the probe is of low intensity, suitable for the purpose of detection and not for pulling or tractive force.

PRELIMINARY EXAMINATION OF A PATIENT

The tip of the probe is first applied to the closed lid. If a ready response is obtained, the search is continued in this manner, the probe being moved along the surface until the surface localization is determined by observing where the peak indication occurs. If no immediate

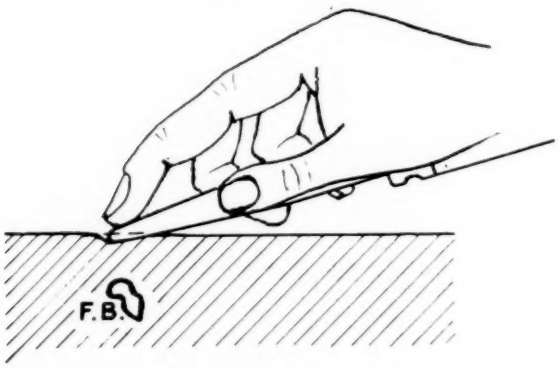

Fig. 5.—Foreign body barely within range. The probe is pressing into the tissues and pressure relaxed in regular rhythm.

response is obtained, the probe is pressed into the tissues, as shown in figure 5, in order to effect a closer approach to the foreign body.

As shown in the illustration, the probe is not held in the normal manner, by its handle, but is held close to the tip, and the tip is pressed into the tissues directly with the forefinger so as to avoid bending of the tip. This is important, for should the tip bend sufficiently to make contact with the internal sensitive element it might result in a response similar to the approach of metal, leading to what is termed "pressure error." Normally, the outer shield will withstand about 1 pound (453 Gm.) of sidewise pressure before deflecting sufficiently to make contact with the internal element. A much greater pressure can be withstood safely head on against the tip.

The probe is pressed in and pressure relaxed in regular rhythm of about 1 second per cycle; if there is a foreign body within range beneath the surface, the indicator response will rise and fall in the same rhythm and in exact synchronism with the motion of the probe. The peak

position is determined by repeating these pressure cycles progressively from point to point along the surface and choosing the point where a maximum response is obtained. If sufficient response is obtainable, a final check is made, in the same manner, with the probe held perpendicular to the surface, for maximum accuracy in localization.

This search must be carefully conducted along the entire orbital rim.

Where a peak indication is obtained, the probe is held against the lid at that point, and the patient is instructed to open his eye and to rotate the eyeball alternately in the several different directions. A consistent change in response with movement of the globe indicates at once that the foreign body is intraocular or is in tissues associated with movements of the eye. If no change in response takes place with rotation of the eyeball, the foreign body is extraocular.

If no response at all is obtained, a magnetic foreign body, if one is known to be present, is beyond range from the surface, and initial exposure must be made with the aid of roentgenologic information alone. In the operating room, after the exposure has been extended sufficiently to bring the probe within range, the probe is used for the final localization, to determine the site for incision.

PROCEDURE IN THE OPERATING ROOM

Sterilization.—Sterilizable rubber jackets of surgical rubber are provided with the instrument to render the probe sterile. These are 16 inches (40 cm.) long, are accurately fitted and extend from the tip of the probe to well beyond the handle. The rubber jackets may be sterilized by either boiling or autoclaving and are handled in the same manner as surgeon's gloves. To insure ease of application over the probe, they must be thoroughly dry inside and out. No part of the probe itself is boilable.

Adjustment of Locator.—The Locator is placed several feet from the operating table; the necessary connections are made, and the controls are turned on and adjusted in accordance with the operating instructions for the instrument. For localization of intraocular bodies the tip portion of the external shield of the probe is unscrewed, so that the smaller diameter of the internal element may be utilized and closer approach to the foreign body made possible. The bare element must always be covered with a rubber jacket, whether sterile conditions are required or not.

It is best to employ an assistant, when available, to handle the Locator and the probe. This avoids the necessity of laying the probe down on the table, from which it may fall and be damaged while the surgeon is otherwise engaged.

Magnets.—When used, magnets must be at least 6 feet (180 cm.) away from the Locator probe. A magnetized probe requires demagnetization in order to be restored to full usefulness. Magnetization of the probe is recognized by sudden reduction in sensitivity and extreme difficulty in tuning the Locator.

The Operator.—After adjusting the Locator, the operator scrubs and wears a sterile gown and gloves. While an unsterile assistant holds the probe, suspended by its cable, the operator applies a sterile rubber jacket over the probe and grasps it by its handle. The operator may then make his other hand unsterile for the purpose of manipulating the Locator controls and for keeping the unsterile probe cable clear of the field.

The Operating Table.—An operating table of wood or other nonmetallic material is highly desirable. When a metal operating table is used the field must be raised at least 15 inches (38 cm.) above the table, using sandbags, pillows or other nonmetallic material. This is particularly important when a foreign body cannot be detected preoperatively from the surface, in which case the necessity for this precaution must not be underestimated. When a strong response is obtained preoperatively and there is no likelihood of fragmentation of the foreign body, so that only low sensitivity will be required in the operation of the Locator, a distance of 8 to 10 inches (20 to 25 cm.) from the operating table will suffice.

Metallic Instruments.—After the preoperative localization has been made, the patient is prepared for the operation. All metallic instruments such as towel clips and hemostats, must be at least 5 inches (12 cm.) from the field.

Even the so-called nonmagnetic speculum often has sufficient influence to affect the Locator indications. This can readily be checked before operation. It may be removed from the field while the probe is being used and replaced afterward. Retractors must be nonmetallic; boilable lucite is an ideal material, but wooden tongue depressors or traction sutures are satisfactory.

Surface Localization with Adequate Exposure.—If at all possible, the operative site should be exposed so as to permit the use of the probe perfectly perpendicular to the surface of the eye, as shown in figure 6.

Surface localization under these conditions is simple and accurate. The site for incision is beneath the center of the probe tip, where the "peak" indication is obtained.

Guarding Against Pressure Errors.—Pressure against the surface must be limited to a minimum; yet contact with the surface must be maintained at all times. For all intraocular work, the probe is

used with the shield of the probe tip removed and the sterilizable rubber jacket covering the bare element. Besides providing protection for the sensitive element, the rubber jacket also serves to provide a smooth, nonabrasive surface for use against the ocular tissues. The probe is grasped near the tip, and the hand is steadied against a nearby surface to facilitate the delicate handling of the probe required for this work (fig. 6). With reduced sensitivity of the Locator and with light contact against the surface, there should

Fig. 6.—Localization of an intraocular foreign body. The shield of the probe tip is removed; the sterilizable rubber jacket covers the bare element; the probe is grasped near the tip, and the hand is steadied on a nearby surface for delicate handling.

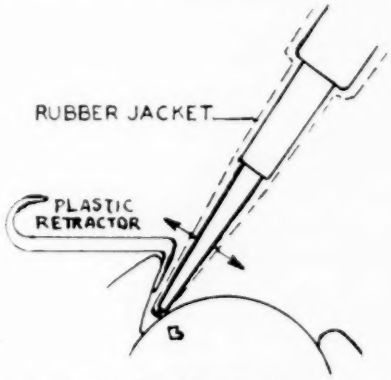

Fig. 7.—Intraocular foreign body with difficult exposure. The arrows indicate direction of movement of the probe to determine whether the foreign body is intraocular or extraocular.

be no false indications due to pressure only. The operator checks this point at once by applying the probe to the gloved hand with the same degree of contact pressure and the same kind of movement that is required in the localization.

Localization with Difficult Exposure.—When conditions do not permit complete exposure of the operative site, and localization is required in a partly closed space, as shown in figure 7, the accuracy

is somewhat less than that possible under conditions of complete exposure. With the shield of the probe removed, the peak position is practically opposite the tip of the magnetic core, as shown in figure 6. It should be noted that with the shield of the probe in place the peak position is about 6 mm. from the tip.

Check for Extraocular Foreign Body.—After the surface localization is obtained under the conditions shown in figure 7, the probe is moved several times from the globe toward the orbit and back again, as shown by the arrows in the illustrations. If the foreign body is extraocular, the Locator indication will increase as the probe moves from the globe toward the orbit. On the other hand, if the Locator indication increases each time the probe is moved back toward the globe, the foreign body is intraocular. For this manipulation of the probe in particular retraction must be sufficient to permit the probe some free space for moving back and forth without undue pressure against the tip. To check against possible pressure errors in the indications, the probe should be manipulated in about the same manner against the gloved hand; and if any appreciable response results, localization must be repeated with the pressure faults corrected.

All-Clear Test.—After a foreign body is extracted, the probe is reapplied to the wound with the instrument set for maximum sensitivity in order to check on whether the wound is clear of all metallic fragments.

CONCLUSIONS

1. The Berman Locator has been in use over two years at the New York Eye and Ear Infirmary, where its value has been increasingly appreciated, as it is absolutely accurate in localizing magnetic foreign bodies. It is compact, portable and easy to operate, can be used in the operative field and is always available.

2. It distinguishes between a magnetic and a nonmagnetic foreign body, and it indicates the quality and quantity of magnetism.

3. While it can be used independently of roentgenologic localization, it has greater value when combined with the latter.

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VASCULAR BASIS OF ALLERGY OF THE EYE AND ITS ADNEXA

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ALLERGY of the eye is, of necessity, a subdivision of allergy of the body as a whole. It is also a subdivision of hypersensitivity. Clinically, urticaria, asthma and iritis or any other allergic lesion of the eye are very different; basically, they must have the same pathologic physiology. The clinical symptoms, signs and pathologic manifestations of allergy depend on the structure of the tissue which is the seat of the allergic reaction.

In 1935 Woods [1] presented his monograph on the place of allergy and immunity in ophthalmology. This work deals with experimental studies in general ocular immunology; the relationship of allergy to focal infection, vernal conjunctivitis, trachoma, syphilis and tuberculosis; the antigenic properties and reactions of lens protein and uveal pigment, and the use of nonspecific proteins, autoserums, vaccines and specific serums in therapy. Woods's monograph is an excellent introduction to allergy of the eye from the viewpoint of a bacteriologist and an immunologist.

Woods mentioned that "the term 'allergy' is now generally used to denote any form of hypersensitiveness not falling under the strict definition of anaphylaxis and is . . . essentially a term of convenience." According to the authorities he cited, the anaphylactic shock hormone is either histamine or a histamine-like substance. The union of antigen and antibody, taking place in a few or in many cells, results in cell injury. Since allergy and hypersensitiveness may both be part of anaphylaxis, it is probable that this hypothetic, nonspecific histamine or histamine-like substance is of fundamental importance in any study of allergy.

In 1940 Appelbaum [2] presented a concise article on allergy of the eye. His conclusions were as follows:

> Present knowledge of experimental and clinical allergic phenomena of the eye makes it necessary for the ophthalmologist to keep in mind "hypersensitivity" as an etiologic factor in many common ocular conditions. Allergy no longer con-

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Submitted as a candidate's thesis in partial fulfilment of the requirements for membership in the American Ophthalmological Society.

1. Woods, A. C.: Allergy and Immunity in Ophthalmology, Baltimore, Johns Hopkins Press, 1935.

2. Appelbaum, A.: Allergic Phenomena in Ophthalmology, Arch. Ophth. **24:** 803 (Oct.) 1940.

cerns the immunologist alone. The practical application of this knowledge, however, is restricted to: (1) the therapeutic use of tuberculin in tuberculosis of the eye; (2) the therapeutic use of uveal pigment in sympathetic ophthalmia and (3) desensitization of patients with cataract who are sensitive to lens cortex with lens protein prior to extraction of cataract.

I agree with his statement that "allergy no longer concerns the immunologist alone" but cannot subscribe to his other conclusions.

In 1941 Bab [3] published a paper in which a philosophic attitude toward allergy was presented. Bab noted that "noninflammatory, edematous swellings are often characteristic of allergic states," that "an allergic person knows whence the trouble arises" and that "draught is often said by patients to be the cause of an external eye disease." Bab also quoted Boyd concerning the role of histamine in allergy. Boyd [4] said:

. . . it is possible that the union of the antigen and antibody acts like an irritant with the liberation of histamine, thus bringing allergic inflammation into line with ordinary inflammation.

Bab also mentioned that "allergic processes are said to be due in greater part to vascular spasms." However, Bab's article deals in the main with the ocular allergies arising from pollens, drugs used externally and foods. Less is said of those forms of allergy not attributable to specific antigen-antibody reactions.

A few months later, in 1941, Bothman [5] published his comprehensive and instructive article on allergy of the eye and its adnexa. This paper deals with reactions to allergins (foods and pollens) and to drugs, chemicals and cosmetics. A consideration of allergy to cold was purposely omitted by him. Bothman stated that in the allergic attack "an antigen-antibody reaction occurs and frees a histamine-like substance which leads to capillary dilatation, increased permeability of vessel walls and an exudation of serum which contains toxic substances. This is the allergic reaction." There are 27 cases in this article illustrative of allergic responses in the conjunctiva, lids, cornea, iris, optic nerve and extraocular muscles, and there is also a discussion of migraine, allergic glaucoma and allergic cataracts.

In 1942 Lemoine [6] published a short article on allergy of the eye, in which the role of the endocrine glands in allergy was emphasized. He said:

. . . it would seem that the allergic patient has lowered thyroid function, intermittent loss of sodium and water, edema of shock organ tissues, lowered blood

3. Bab, W.: Am. J. Ophth. **24**:759 (July) 1941.

4. Boyd, W.: A Textbook of Pathology, ed. 2, Philadelphia, Lea & Febiger, 1935.

5. Bothman, L.: The 1941 Year Book of the Eye, Ear, Nose and Throat, Chicago, The Year Book Publishers, Inc., 1941, pp. 7-58.

6. Lemoine, A. N.: Allergies in Ophthalmology, Arch. Ophth. **28**:79 (July) 1942.

pressure, parasympathetic hyperstimulation, a low blood sugar content and an increase of cholesterol, urea and amino acids.

He noted that hypofunction of the thyroid gland and the adrenal cortex can account for these changes, while the secretions of the adrenal medulla and the posterior lobe of the pituitary tend to offset these pathologic physicochemical changes.

In accordance with the newer concept of allergy, Lemoine mentioned that histaminase seems to be of benefit in some cases of food allergy. He apparently agreed with Elschnig and Woods that sympathetic ophthalmia is due to hypersensitivity to uveal pigment, and he seemed to favor treatment with tuberculin for ocular lesions attributed to tuberculosis.

Most of the aforementioned authors were concerned with the antigen-antibody reactions which give rise to the allergic lesion. Also, most of them stated that either histamine or a histamine-like substance is both the result of the antigen-antibody reaction and the direct cause of the allergic lesion.

Because histamine is a chemical body of known composition, because it has a profound effect on capillary endothelium and smooth muscle, because it is the probable cause of physical allergy in many cases, because it occurs in the body and because it is formed in or accumulates in the body under certain well known conditions, it is my belief that a discussion of allergy from the viewpoint of the etiologic importance of histamine or histamine-like bodies would be complementary to the studies of the authors cited thus far in this article.

Owing to the long domination of medicine by bacteriology, there is a widespread belief that because certain micro-organisms produce certain diseases with monotonous regularity similar allergic lesions must always have the same cause, whether it be a streptococcus, a focus of infection, a specific antigen or a virus. Allergy, immunology and anaphylaxis have been the special province of bacteriologists for so many years that the average physician in practice is scarcely permitted the right to an opinion about these matters. Dead bacteria or their products have been introduced parenterally in varying amounts into every part of the body. A special esoteric terminology has been developed, which is understood only by the allergists and immunologists. Many of these investigators are not physicians, but they speak authoritatively about clinical lesions despite the fact that most of their work has been limited to experiments on healthy animals.

Much valuable work has been done by the bacteriologists and the immunologists in the past, particularly with regard to diseases due to micro-organisms. However, many problems cannot be solved by the bacteriologic immunologic approach, and I think that allergy is one of them. Despite all the remarkable advances which have been claimed for allergy in recent years, it is my opinion that very little of practical value

to ophthalmologists has been discovered. All ophthalmologists can recall many cases of iritis or choroiditis in which all "foci of infection" were investigated, teeth were removed, tonsils were removed, the prostate was massaged, the reactivity to allergens was determined, the diet was changed and, as a final gesture, injections of tuberculin were given for weeks, months or years. In the course of weeks or months the lesion subsided, and the "cure" was attributed to the tuberculin or to the removal of the teeth or tonsils. In other cases no foci of infection were removed, no tuberculin was given and the lesion improved in the course of weeks or months with the time-honored remedies. Finally, there are the cases of iritis, acute retrobulbar neuritis and even death which have occurred after the removal of a tooth, the opening of a sinus or the parenteral introduction into the body of vaccines or antiserums for therapeutic or diagnostic purposes. Many such cases have been reported, but many, many more have probably occurred and never been recorded.

The mention of an accident which followed injections of tuberculin is sufficient to indicate the danger inherent in the use of this substance. Muncaster and Allen [7] reported the case of a woman of 31 who had been given 0.00002 mg. of tuberculin (purified protein derivative) intradermally by a school physician. As no reaction had occurred forty-eight hours later, she was given 0.005 mg. For the following ten days the patient felt tired and weak. Then pain, redness, tearing and photophobia developed in the left eye, and a few hours later the right eye was similarly involved. When she was first seen by the authors, she was found to have severe bilateral uveitis. She was hospitalized for three weeks and treated at home for nearly six weeks longer before her vision improved to 20/20. As the vitreous cleared, she was seen to have retinal periarteritis. This was the result of a routine tuberculin test in an apparently healthy adult.

Lockhart [8] recently reported the death of a patient following the intravenous injection of 0.12 cc. of triple typhoid vaccine. After a rise in temperature and in the pulse and respiration rates, shock developed and the patient died, despite the use of epinephrine and nikethamide. Death was due to coronary thrombosis.

To most physicians allergy means "hypersensitivity" to protein, whether of plant, animal or bacterial origin. Therefore cutaneous tests, desensitization, removal of foci of infection and various types of shock therapy make up the diagnostic and therapeutic approach to allergy.

To me, allergy includes all those aseptic or abacterial lesions in which the basic pathologic process can be reduced to the common denominator

7. Muncaster, S. B., and Allen, H. E.: Bilateral Uveitis and Retinal Periarteritis as a Focal Reaction to the Tuberculin Test, Arch. Ophth. **21**:509 (March) 1939.

8. Lockhart, R. J.: Brit. J. Dermat. **51**:318 (July) 1939.

of either increased capillary permeability or excessive contraction (spasm) of smooth muscle or both. Smooth muscle, of course, includes the smooth muscle in the arterioles, as well as in the bronchioles and the gastrointestinal tract. The concept of allergy and its treatment which I propose to develop must include as etiologic factors all influences—chemical, nervous, humoral or climatic—which can cause either increased capillary permeability or smooth muscle spasm or both. Since, except for the muscles of the iris and the ciliary body, most of the smooth muscle in the eye is found in the walls of the arteries and arterioles, I think that allergy of the eye can be interpreted as a problem in vascular physiology. For this reason, most of this article will deal with physiology and biochemistry and with clinical reports. Little reference will be made to animal experiments. No proof will be offered that the lesions to be discussed are allergic except to point out (1) that the basic pathologic process of the lesions can be interpreted as a manifestation of arteriolar spasm or increased capillary permeability or both, and (2) that it is the opinion of some ophthalmologists that the lesions are due to allergy.

If the concept of allergy had originated in 1930 instead of in 1903, it is not unlikely that recent advances in physiology and biochemistry would have made the approach to the problem entirely different. The years between 1910 and 1930 were characterized by remarkable advances in these two important preclinical sciences. However, bacteriology was a vigorous, rapidly growing branch of medical science long before 1903. Because anaphylaxis (experimental fatal allergy in animals) was associated with the injection of bacterial and other proteins into animals, allergy and anaphylaxis became the special protégés of bacteriology.

If the concepts of allergy and anaphylaxis had not evolved until 1930 or 1935, or if the recent advances in physiology had preceded the development of bacteriology, it is not unlikely that the various manifestations of allergy would have been investigated as problems of physiology rather than of bacteriology. Only ten years ago Horder [9] said:

> . . . What was disease but a state of morbid physiology? The functions by which a man lived in health were the same as those through which he expressed his pathologic state.

In a recent article, entitled "The Role of the Terraine in the Development of the Polyneuritides," Lecoq and Vignal [10] stated that the constitution of the "terrain" may depend on racial, hereditary or personal antecedents; on temperament, endocrine type, and the neurovegetative and reticuloendothelial systems; on the state of nutrition and metabolism; on pathologic invasion, and on environmental variations. They

9. Horder: Brit. M. J. **1**:632 (March 25) 1935.
10. Lecoq, R., and Vignal, O.: Presse méd. **48**:331-332 (March 27) 1940.

cited Olmer's statement that except for trauma, accidental intoxications and acute infection there is really no line of demarcation between the normal and the pathologic and that it is often by imperceptible degrees that disease is instituted. Lecoq and Vignal also stated that in some of the avitaminoses the most important factor is not so much the avitaminosis as it is the humoral disturbance resulting from it.

Moreover, Gajdos [11] eight years ago stated that histamine could be considered a specific chemical intermediary between the variability of causes and the identity of the reactions of the organism in hyperergic diseases. He expressed the opinion that histamine is the link between cause and effect in certain morbid processes, giving to the pathogenesis a new orientation, which can be compared with the conception of the role of humoral agents in normal physiology, namely, of epinephrine (or sympathin) as a transmitter of sympathetic impulses and of choline (acetylcholine) as a transmitter of parasympathetic excitation.

Likewise, Albus [12] has suggested, on the basis of physiologic and pharmacologic studies, that the more comprehensive term "histamine-susceptible constitution" be substituted for "allergic constitution."

Tooke and Nicholls,[13] in discussing changes in the fundus associated with cardiovascular hypertension, referred to Ricker,[14] who stated in 1927 that the underlying mechanism of both hypertension and inflammatory conditions is a neurovascular defect. Various stimuli cause a constriction of all terminal vascular segments (arterioles). The capillaries become fatigued and relax, as occurs after an overdose of epinephrine. With constricted arterioles and dilated capillaries there is slowing of the blood stream in the capillary bed. The capillaries next become more permeable, as a result either of lack of oxygen or of opening up of spaces in the capillary walls. Depending on the degree of increased capillary permeability, the type of transudate and the degree of slowing of the blood stream, Ricker differentiated three stages: (1) prestasis, or liquor stasis, in which plasma (and fibrin) are found in the transudate; (2) peristasis, or leukostasis, in which white cells (chiefly lymphocytes) also pass into the perivascular tissues, and (3) stasis, or rubrostasis, in which erythrocytes pass through the capillary walls. Krogh confirmed Ricker's observations. In their simplest forms, it must be apparent that prestasis causes urticarial lesions, peristasis produces lesions characterized by perivascular edema and round cell infiltration and stasis results in purpuric lesions. Lesions attributed to allergy, focal infection, histamine poisoning or overdoses of epinephrine and even

11. Gajdos, A.: Presse méd. **46**:509 (April 2) 1938.

12. Albus, G.: Ztschr. f. d. ges. exper. Med. **108**:592 (March 3) 1941.

13. Tooke, F. I., and Nicholls, J.: Am. J. Ophth. **21**:395 (April) 1938.

14. Ricker, G.: Sklerose und Hypertonie der innervierten Arterien, Berlin, Julius Springer, 1927.

the lesions of B avitaminosis can be interpreted as due to varying degrees of prestasis, peristasis and stasis.

In my opinion, all abacterial lesions designated as manifestations of allergy show varying degrees of prestasis, peristasis and stasis. Moreover, all chemical, nervous or other agents which can cause either arteriolar spasms or increased capillary permeability or both must be regarded as direct or contributing causes of allergy.

Finally, it must be obvious that the only difference between the normal and the allergic person is one of degree. Every one probably has minor or transitory allergic manifestations during life. Allergic patients have more severe and more frequent attacks of allergy. Fundamentally, the differences between the normal and the allergic person are quantitative rather than qualitative.

CURRENT CONCEPTS OF ALLERGY AND ANAPHYLAXIS

Bacterial and Immunologic Aspects.—According to the Seegals,[15] allergy is a condition of hypersensitiveness in human beings. It defines a group of biologic responses in which body tissues have been so altered by previous contact with an antigen that their subsequent reactions to the same inciting agent may be entirely different from those produced by the initial contact. Among the allergic symptom complexes are serum disease and serum accidents, hay fever and asthma, gastrointestinal allergy, skin allergy, drug allergy, physical allergy and bacterial allergy.

It is obvious that if allergies due to drugs and physical agents are to be included in the phenomena of hypersensitiveness the Seegals' definition should be broadened by eliminating all reference to antigen. Their definition is too limited because it focuses undue attention on antigen-antibody reactions.

Beatrice Seegal [16] noted that anaphylaxis is a type of hypersensitivity in animals experimentally produced by the repeated parenteral injection of foreign proteins. For the purposes of this article, I think it may be assumed that allergy and anaphylaxis are fundamentally the same, differing only in degree. Allergy usually disables the patients; anaphylactic shock usually kills the experimental animal.

There are two theories of anaphylaxis, the physical and the chemical. According to the physical theory, the union of antigen and antibody disturbs the colloidal equilibrium of the plasma or the cell protoplasm, which, in turn, so interferes with normal physiologic activity that anaphylactic shock results. According to the chemical theory, a "toxic" substance (anaphylactotoxin) is produced by the union of antigen and

15. Seegal, D., and Seegal, B. C., in Gay, F. P.: Agents of Disease and Host Resistance, Springfield, Ill., Charles C Thomas, Publisher, 1935, pp. 79-112.

16. Seegal, B. C., in Gay, F. P.: Agents of Disease and Host Resistance, Springfield, Ill., Charles C Thomas, Publisher, 1935, pp. 36-78.

antibody. There are many variations of this theory, and many workers think that this toxic substance is liberated not from the injected antibody but from the animal's own antibodies, plasma or tissues. One school believes that this "anaphylactotoxin" is either histamine (Dale) or a histamine-like substance (Lewis).

Topley [17] discussed the histamine origin of hypersensitivity clearly and logically. After mentioning that the symptoms and lesions of anaphylactic shock are constant for a given animal species, irrespective of the nature of the sensitizing antigen, and that they differ sharply from one species to another, he stated:

> Histamine is a relatively simple substance of known chemical constitution. . . . It can hardly be a mere coincidence that on intravenous injection it mimics so closely the syndrome produced by the injection of a nontoxic antigen into a sensitized animal.

After noting that the tissues that play the most dramatic part in anaphylactic shock are exactly those that are sensitive to histamine, he continued as follows:

> . . . Whether the cells that are injured and liberate histamine are themselves histamine-sensitive, whether minimal injury may so disturb the internal economy of cells that it becomes reactive to its own contained histamine, or whether we should locate the injury and liberation of histamine in one type of cell, the response to the liberated histamine in another, are problems which are not soluble at the moment.

He then pointed out that anaphylactoid reactions resemble anaphylactic reactions in that the secondary, histamine-like effect is the same. An anaphylactic or anaphylactoid reaction consists, he stated,

> . . . of a description of cellular injury, differing from case to case according to the reagent employed and the susceptibilities of the experimental animal, and a histamine effect, differing from one animal species to another according to the distribution of the histamine-sensitive cells but common to all reactions in one animal species by whatever reagents they are caused.

In his summary, he stressed the point that the most dramatic features of anaphylactic shock are the result not of the antigen-antibody reaction itself but of the liberation of histamine by the injured cells and the secondary response of the histamine-sensitive cells throughout the body.

Findlay [18] also showed that subcutaneous injections of histamine caused the localization of pathogenic bacteria and filtrable viruses (which were injected intravenously) at the site of the injections of histamine. He attributed this localization to capillary dilatation and increased capil-

17. Topley, W. W. C.: An Outline of Immunity, Baltimore, William Wood & Company, 1933, pp. 192-223.

18. Findlay, G. M.: J. Path. & Bact. **31**:633 (Oct.) 1928.

lary permeability. Topley [19] also noted that a diminished oxygen supply to tissues allowed organisms to grow better. This suggests that bacterial invasion of tissues may be secondary to circulatory impairment, especially when relatively nonvirulent micro-organisms are the invaders.

Beatrice Seegal [16] noted Drinker and Bronfenner's report that amyl nitrite relieved anaphylactic shock in the rabbit. She also mentioned that rats are refractory to anaphylaxis and must be kept on a diet deficient in vitamin B before shock can be induced. Rats can be sensitized if the adrenal glands are removed. Thyroidectomized guinea pigs cannot be actively sensitized. She further noted that all the pathologic and physiologic manifestations of anaphylactic shock may be referred to contraction of smooth muscles and increased capillary permeability. It is of some interest that in 1914 Mautner and Pick,[20] in treating anaphylactic shock, obtained good results from the vasodilating action of nitrites. This agrees with the work of Drinker and Bronfenner. In both observations therapy was directed toward smooth muscle spasm rather than desensitization.

Physiologic Aspects.—Evans [21] stated that Dale and his co-workers have reported that in the cat histamine causes arteriolar constriction, capillary dilatation, increased capillary permeability, edema and hemoconcentration. Plasma, white cells and even red cells pass out into the tissues. Capillary tonus is better maintained, however, in the presence of well oxygenated blood containing minute amounts of epinephrine. According to Landis,[22] lack of oxygen in the circulating blood causes the same capillary changes.

In 1910, and again in 1919, Dale and Laidlaw [23] commented on the similarity between histamine shock and anaphylactic shock. In 1929 Dale [24] concluded that the intracellular antigen-antibody reaction causes intracellular injury which liberates histamine and other substances. These "other substances" may account for the signs which are observed in anaphylactic, but not in histamine, shock.

In 1931 Best and McHenry [25] reviewed the physiologic aspects of histamine in an article based on over 400 original references. They mentioned that histamine can be obtained from nearly all the tissues

19. Topley,[17] pages 248-249.

20. Mautner and Pick, cited by Sollmann, T.: A Manual of Pharmacology, ed. 2, Philadelphia, W. B. Saunders Co., 1922, p. 446.

21. Evans, C. L.: Recent Advances in Physiology, ed. 4, Philadelphia, P. Blakiston's Son & Co., 1930.

22. Landis, E. M.: Physiol. Rev. **14**:404 (July) 1934.

23. Dale, H. H., and Laidlaw, P. P.: Histamine Shock, J. Physiol. **52**:355, 1918-1919.

24. Dale, H. H.: Lancet **1**:1179 (June 8); 1233 (June 15); 1285 (June 22) 1929.

25. Best, C. H., and McHenry, E. W.: Physiol. Rev. **11**:371 (Oct.) 1931.

of the body (skin, intestinal mucosa, intestinal contents, white blood cells, feces, muscle, lung, liver, spleen, brain and nervous tissue). It is probably the substance of Lewis, and it is set free by antidromic nerve impulses, axon reflexes and trauma. Certain gram-negative bacteria produce it from histidine by decarboxylation. It is produced in the skin as a result of exposure to cold air or cold water and also by ultraviolet irradiation. While histamine may be fatal if given intravenously in even small amounts, the body apparently can neutralize it, since large quantities may be formed in or introduced into the intestine without causing symptoms. Its removal is probably oxidative, either directly or through the mediation of histaminase. Oxygen accelerates the histamine-histaminase reaction, and oxygen seems to be a physiologic antidote for histamine.

For the guinea pig, which is most susceptible to anaphylactic shock, the approximate minimal lethal dose is about 0.3 mg. of histamine per kilogram of body weight; for the white rat, which is almost immune to anaphylactic shock, the minimal lethal dose is 300 mg. per kilogram of body weight. This last fact supports indirectly the theory that anaphylactic shock and histamine are closely related.

Moon [26] notes that in 1911-1912 Dale and Laidlaw [27] stated the belief that the action of histamine typifies the effects of a large class of substances. These include bacteria and their products, extracts of various tissues, foreign serums and other proteins, and peptones and other products of protein cleavage. All these apparently unrelated substances have one feature in common: They injure the capillary endothelium.

Moon also noted: [26]

> . . . suitably large doses of adrenaline [epinephrine] will produce a condition of circulatory failure indistinguishable from shock. . . . Adrenalin may produce maximal arterial constriction of such degree that the tissues suffer from anoxia. If the lack of oxygen is of sufficient duration and degree, atony of the capillaries and venules will develop in the areas affected.

He also mentioned that Cannon had endorsed this as the probable explanation of circulatory failure following injections of epinephrine and had suggested that overactivity of the sympathicoadrenal system is a factor resulting from pain, strong emotions and other conditions.

From the preceding paragraph it must be apparent that epinephrine, which in small doses is a physiologic antogonist of histamine, in large doses is a synergist, since the two substances cause the same arteriolar

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26. Moon, V.: Shock and Related Capillary Phenomena, New York, Oxford University Press, 1938.

27. Dale, H. H., and Laidlaw, P. P.: J. Physiol. **41**:318, 1910-1911; **43**:182, 1911-1912.

and capillary changes. This fact may explain why allergic patients become "epinephrine fast."

Moon, of course, referred to a general shocklike condition which resulted from intravenous injection of epinephrine. In 1940 Cohen and Waterstone [28] noted that local changes occurred in the skin after injections of epinephrine. They reported the cases of 2 Negro women with asthma in whom an area of edema developed at the site of intradermal and subcutaneous injections of epinephrine, followed by local tissue necrosis. These authors compared the lesions to the Arthus phenomenon. From their description, the lesions also resembled a strongly positive tuberculin reaction. They attributed the lesions to anaphylaxis. Obviously, they can be attributed to physiologic reactions which were pathologic in degree.

It may be recalled that Gajdos [11] stated that histamine was the link between cause and effect in certain allergic processes.

Corelli [29] reported that the subcutaneous injection of 0.8 or 1.0 mg. of histamine in 14 cases of erythema nodosum attributed to rheumatic fever or tuberculosis intensified the preexisting lesions and caused the appearance of new lesions. Moreover, it intensified positive reactions to subcutaneous and intradermal tuberculin tests. Possibly the tuberculin test is really a test for hypersensitivity to histamine!

It should also be pointed out that histamine is effective in minute amounts. Pickering [30] produced headache by injecting 0.1 mg. intravenously, and Maijala [31] reported a case in which the patient died after receiving 0.8 mg. subcutaneously. Moreover, Peters and Van Slyke [32] said:

> . . . Dale, Abel and their associates have shown that it [histamine] is not only highly toxic, but that it has, in minute amounts, such effects on blood pressure, on the contractibility of smooth muscle and on capillaries that it may, perhaps, be classed with the hormones.

In 1941, Urbach, Herrman and Gottlieb [33] discussed hypersensitiveness to cold, noting that this may be due to an effect of histamine. They stated:

> . . . under given pathologic conditions the tissue's own protein can undergo alteration, and under the influence of physical agents this altered protein produces

28. Cohen, A. E., and Waterstone, M. L.: J. Allergy **11**:393 (May) 1940.

29. Corelli, F.: Policlinico (sez med.) **44**:491 (Oct. 1) 1937.

30. Pickering, G. W., and Hess, W.: Brit. M. J. **2**:1097 (Dec. 17) 1932.

31. Maijala, P.: Nord. med. tidskr. **16**:1287 (Aug. 13) 1938.

32. Peters, J. P. and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1931, vol. 1, p. 398.

33. Urbach, E.; Herrman, M. F., and Gottlieb, E. M.: Cold Allergy and Cold Pathergy, Arch. Dermat. & Syph. **43**:366 (Feb.) 1941.

a histamine-like substance which elicits, for instance, cutaneous manifestations. Under the heading of cold pathergy, they stated:

> Predisposing factors, such as previous infections and other diseases, can bring about a certain degree of instability in the peripheral neurovascular system. Physical agents are thus enabled locally to elicit abnormal neurovascular reactions.

They also state that "not in every case of hypersensitiveness is the condition to be considered as allergic, i. e., based on antigen-antibody reaction."

Later in the same year Harkavy [34] emphasized the role of the blood vessels in bronchial asthma with these words:

> . . . Since, therefore, the blood vessels appear to be the primary site of the allergic reaction, it may be reasoned that any organ in the body may become a shock tissue if the blood vesssels supplying it have become sensitized.

In some of his cases, in addition to the pulmonary lesions, there appeared hyperergic vascular lesions in the skin, such as hemorrhagic necrosis (1 case), purpura, urticaria and angioneurotic edema (4 cases) and periarteritis nodosa (1 case). After mentioning the property of histamine-like substances in initiating smooth muscle spams and increased capillary permeability, he stated that the hemopoietic tissues also participated in the generalized allergic response and that "the bone marrow may therefore be regarded as a shock organ which may react under allergenic stimulation by multiplication of its cellular elements or by suppression." (In other words, agranulocytosis, leukopenia, leukocytosis, eosinophilia and even leukemia may all be due to the same type of stimulus, but quantitative variations in the stimulus and the response of the bone marrow account for marked variations in the hemogram (W. F. D.).

Harkavy concluded that not only the bronchi but the myocardium, serous membranes, joints, skin and nervous and hemopoietic systems may be involved in the more generalized vascular reactions and that distinct syndromes may arise which may be reversible or irreversible. He expressed the belief that the various lesions in his cases represented hyperergic vascular responses.

All the available evidence indicates that allergy resembles a localized manifestation of histamine poisoning. Tiny amounts of histamine may be of physiologic importance in regulating capillary permeability. In large amounts histamine acts as a "toxin" by increasing capillary permeability beyond physiologic limits. It causes tissue anoxia. Lack of oxygen can cause the same type of lesions. Oxygen is a physiologic antagonist of histamine. All agents which can cause increased capillary permeability and tissue anoxia may be concerned in the production of allergic lesions. As Moon [26] has said: ". . . many phenomena called

34. Harkavy, J.: Vascular Allergy, Arch. Int. Med. **67**:709 (April) 1941.

toxic are essentially anoxic." Allergy must be included among these phenomena.

It is not unreasonable to assume that any factors which would tend to relieve capillary and tissue anoxia should be of value in the treatment of allergy.

FOCAL INFECTION AND ALLERGY

It is impossible to discuss allergy without mentioning focal infection because of the belief of many allergists that the subject becomes sensitized to bacterial products which are formed in the focus and later transported by the blood stream to other parts of the body. Countless experiments have been done on healthy animals to prove that ocular lesions are due to distant "foci of infection" and that "elective localization" is a fact, rather than just a hypothesis. It is true that removal of foci of infection is sometimes followed by subsidence of an ocular lesion. It is also true that in many instances the ocular lesion is not affected by such an operation, and in a few instances the removal of a tooth or the "cleaning out" of a sinus is followed by the development of an ocular lesion which the operation is supposed to cure.

With regard to surgical procedures on the sinuses for acute retrobulbar neuritis, Benedict [35] reported that operations on normal sinuses were fully as effective as operations on diseased sinuses. He concluded that this therapy was nonspecific and that improvement could be attributed to the hyperemia resulting from the trauma and the absorption of blood. In other words, the operation acts by means of autohemotherapy and is similar to foreign protein therapy.

Schmidt [36] came to the same conclusion regarding the removal of infected dental roots for chronic iridocyclitis and other conditions. He broached the question as to whether or not the loss of blood, its absorption and the necrosis of tissue following dental treatment might be the equivalent of nonspecific parenteral foreign protein therapy.

Charlin [37] pointed out that ocular lesions attributed to dental infection contained no germs.

Lagrange and Goulesque [38] expressed the opinion that foci of infection in the teeth and sinuses act reflexly by causing antidromic impulses via the sensory fibers of the fifth nerve, either by axon reflexes or by overaction of the sympathetic nervous system, to cause ocular lesions. However, they asserted that hematogenous transfer of the exciting agent can explain lesions of the eyes due either to near or to distant primary

35. Benedict, W. L.: Retrobulbar Neuritis and Disease of the Nasal Accessory Sinuses, Arch. Ophth. **9**:893 (June) 1933.

36. Schmidt, K.: Klin. Monatsbl. f. Augenh. **93**:191 (July) 1934; abstracted, Arch. Ophth. **13**:887 (May) 1935.

37. Charlin, C. C.: Arch. de oftal. de Buenos Aires **11**:251 (May) 1936.

38. Lagrange, H., and Goulesque, J.: Ann. d'ocul. **175**:493 (July) 1938.

foci of infection. Their 3 patients with iridocyclitis improved only after operation on the sinuses. Two of their patients were receiving antisyphilitic treatment at the same time. Their patients probably improved for the reasons suggested by Benedict and by Schmidt as to the modus operandi of removal of foci of infection.

In 1918 Evans [39] stated:

> [in cases of iritis, iridocyclitis, choroiditis, retinitis, retrobulbar neuritis and postoperative iridocyclitis] no organisms have been found in the blood or in the [anterior] chamber in these cases and truth to tell we have not yet been able to prove conclusively their bacterial origin.

In 1933 Evans,[40] after pointing out the defects in the theory of focal infection, suggested:

> . . . (*a*) Secondary lesions result primarily from "lowered vitality or resistance" of the tissues secondarily affected. (*b*) Lowered vitality is due to defect of "trophic influence" or to reflex antidromic impulses. Antidromic impulses appear to dislocate vascular reflexes and cellular activity. (*c*) The vascular reflex is an essential factor in the maintenance of sympathetic balance, though probably other undetermined factors are also concerned. (*d*) The vascular state of the tissues can be influenced through short and long axon-reflexes. The short axon-reflex is salutary and protective. The long axon-reflex, antidromic and noxious, accounts for the incidence of the secondary lesion on the same side as the primary lesion.

There is much truth in the conclusion of Evans, and he deserves credit for trying to explain the lesions attributed to focal infection as manifestations of disordered physiology, rather than confusing the issue with ultrascientific, but clinically obscure, words and phrases. Since antidromic impulses liberate histamine, it will become apparent that his approach and my approach to this subject of allergy have much in common.

It has been said that the teeth, tonsils and sinuses are the favorite points of operative attack because they are readily accessible. The lower part of the gastrointestinal tract is loaded with micro-organisms of the colon group of bacilli (which are known to produce histamine). Certainly, this region of the body must be considered in any theory of focal infection. A praiseworthy note of caution with regard to operations on "foci of infection" was recently sounded by Reimann and Havens.[41] After a comprehensive survey of the literature, these authors stated:

> . . . in the light of present knowledge, the removal of such local infections in the hope of influencing remote or general symptoms and disease must still be regarded as an experimental procedure not devoid of hazard.

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39. Evans, J. J.: Birmingham M. Rev. **83**:1 (Jan.-Feb.) 1918.
40. Evans, J. J.: Birmingham M. Rev. **8**:252 (Dec.) 1933.
41. Reimann, H. A., and Havens, W. P.: Focal Infection and Systemic Disease: A Critical Appraisal, J. A. M. A. **114**:1 (Jan. 6) 1940.

"SHOCK" THERAPY OF ALLERGIC DISEASES

As mentioned in the preceding section, operations on foci of infection can be interpreted as equivalent to nonspecific parenteral foreign protein therapy or to autohemotherapy. For many years intravenous injections of typhoid vaccine and intramuscular injections of boiled milk have been the favorite weapons for combating allergic inflammations of the uveal tract, optic nerve and cornea. As a modification of this therapy, diphtheria antitoxin is used in treatment of sympathetic ophthalmia, and vaccines other than typhoid are given subcutaneously for a host of conditions.

Except for the fact that the patient knows something is being done to him, it is still a question in my mind as to the real value of these procedures. Moreover, they are not devoid of danger, and when used for extraocular lesions they have been known to produce the type of lesions which they are supposed to cure. Furthermore, death has occasionally occurred after any one of the types of shock therapy for ocular, as well as extraocular, lesions.

Ten years ago Irons [42] collected 140 instances of harmful results, including a number of cases of death, following subcutaneous injection of vaccines. In 17 cases asthma occurred in persons not previously known to have suffered from the condition. Irons noted that Benedict and Rucker reported that foreign protein therapy seemed to be most effective with patients seen early in a first attack of iritis rather than with patients whose disease had been active for several months or patients who had suffered from previous attacks. As Irons said: [42]

> . . . there is noted a group of favorable cases in which from the natural history of the disease improvement would be most likely to be expected.

Furthermore, in discussing arthritis, both atrophic and hypertrophic, which has been compared with iritis and scleritis by many ophthalmologists, Irons said: [42]

> . . . While infection is believed by some to be one of the chief factors responsible for the former of these two [atrophic type], in both groups other factors including heredity, poor nutrition, metabolic disturbances [and] impaired local blood supply . . . to mention but a few, play a large part in the production of joint disease and disability.

In an earlier section of this article, reference was made to Lockhart's [8] case, in which death followed intravenous injection of triple typhoid vaccine and to Muncaster and Allen's [7] case, in which bilateral uveitis and periarteritis developed after routine tuberculin test. Sédan and Koutseff [43] reported an allergic reaction of the iris following urethral dilation in a man of 56 who had a chronic periurethral infection and who had previously had several attacks of acute iritis. I can recall 2

42. Irons, E. E.: Bull. New York Acad. Med. **7**:412 (June) 1931.

43. Sédan, J., and Koutseff, A.: Ocular Allergy: New Observations, Arch. Ophth. **22**:924 (Nov.) 1939.

similar cases, as well as a case in which acute iritis developed in less than forty-eight hours after removal of an "infected" tooth.

Brown [44] mentioned that 20 per cent of 75 patients with diphtheria who had received diphtheria antitoxin had papilledema and 10 per cent complained of "blurriness" of vision. He ascribed the lesions to vascular dysfunction.

Theodore and Lewson [45] reported the case of bilateral fibrinous iritis which devoloped as an accompaniment of serum sickness twenty-two days after the patient had received 80,000 units of type I antipneumococcus serum intravenously. The patient also had had serum sickness nine days after receiving the serum. These authors mentioned Brown's report; Mason's report, in which 3 patients had optic neuritis after receiving antiserums, and Bedell's case, in which bilateral retinal edema with hemorrhages developed after an injection of tetanus antitoxin. Theodore and Lewson's patient did not respond to administration of ephedrine by mouth and instillations of epinephrine in the eyes, but he did respond rapidly to atropine and hot compresses.

Similar reactions to vaccines, antiserums and injections of foreign protein, both ocular and extraocular, have been reported so often that a monograph could be written on this phase of the subject alone. All are probably manifestations of vascular dysfunction, due to varying degrees of arteriolar spasm and increased capillary permeability, with resulting tissue anoxia.

Moon [26] stated that severe reactions following foreign protein therapy are probably due to arteriolar constriction, followed by arteriolar relaxation. Insulin, metrazol and other types of convulsive therapy probably act similarly, but it is not the arteriolar constriction but the succeeding arteriolar dilatation (which occurs just this side of death) which is responsible for the beneficial results in the treatment of nervous and mental diseases reported by many authors.

Even heat therapy, which is fashionable at the moment, and which is basically similar to foreign protein therapy and probably fully as dangerous, is used at times in treating allergic ocular lesions. Histamine may be the culprit here. Many workers have postulated that histamine is the cause of shock following severe burns. Hildebrandt [46] recently reported that both diathermy and short wave therapy increased the histamine content of the blood by several hundred per cent in animal experiments.

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44. Brown, A. L.: Am. J. Ophth. **8**:614 (Aug.) 1925.

45. Theodore, F. H., and Lewson, A. C.: Bilateral Iritis Complicating Serum Sickness, Arch. Ophth. **21**:828 (May) 1939.

46. Hildebrandt, F.: The Pharmacology of Short Waves, J. A. M. A. **112**: 1274 (April 1) 1939.

Warren, Carpenter and Boak [47] reported that herpes developed in 46.2 per cent of 411 patients given 545 treatments with fever artificially induced by physical methods. In 3 of the patients herpetic lesions of the cornea, and in 2 congestion of the sclera, developed. Fifteen of the group with herpes showed mild symptoms of meningoencephalitis, and 8 patients without herpes had symptoms of meningoencephalitis. In 2 patients (not in this series) delusional states developed; 1 required restraints for two days. These authors attributed the herpes to a virus! Why not histamine?

Ebaugh, Barnacle and Ewalt [48] reported that there were 399 delirious reactions in 350 patients who had received 2,585 treatments in the Kettering Hypertherm. The average duration of the reactions was about one hour. Ten patients had severe reactions. The authors concluded that "fever exaggerates the subject's outstanding personality characteristics."

Suppose that heating the tissues does produce an increase in histamine, and suppose it does cause "mental episodes" to occur. Is there any evidence that "mental episodes" which are not due to artificial fever therapy are produced by histamine? The literature supplies some evidence.

As early as 1933 Watt [49] suggested that histamine toxemia (probably of intestinal origin) was the cause of severe mental depression.

In 1934 Davidson [50] discussed acute death in 22 "excited" patients with mental disease; death was attributed to "exhaustion." Various organs, including the central nervous system, showed edema and congestion. He attributed the lesions to "capillary toxicosis," endogenous in origin, and concluded: ". . . we may perhaps identify them [the toxic substances] with the H-substance of Lewis."

Shulack [51] confirmed the observation that cerebral congestion was the presenting pathologic feature in these cases, and in an editorial in the *British Medical Journal* [52] it was stated that Jahn and Greving had noticed a similarity between these pathologic changes and histamine poisoning in animals.

Collins [53] reported the case of a patient with mild disseminated sclerosis who became paralyzed in all four limbs and anesthetic over

47. Warren, S. L.; Carpenter, C. M., and Boak, R. A.: J. Exper. Med. **71**: 155 (Feb.) 1940.

48. Ebaugh, F. G.; Barnacle, C. H., and Ewalt, J. R.: Psychiatric Aspects of Artificial Fever Therapy, Arch. Neurol. & Psychiat. **39**:1203 (June) 1938.

49. Watt, J. C.: Brit. M. J. **1**:896 (May 20) 1933.

50. Davidson, G. M.: Am. J. Psychiat. **91**:41 (July) 1934.

51. Shulack, N. R.: Psychiatric Quart. **12**:282 (April) 1938.

52. Sudden "Exhaustive" Death in Excited Patients, editorial, Brit. M. J. **2**:751 (Oct. 8) 1938.

53. Collins, R. T.: Bull. Neurol. Inst. New York **7**:291 (Dec.) 1938.

most of the surface of the limbs after his eleventh three hour treatment with the Vapotherm at a temperature of 104 F. Collins noted that anoxia or alkalosis might explain the findings. His final conclusion was:

> . . . Hyperthermia is a powerful therapeutic agent and may do injury to nervous tissue.

In this section, many conditions outside the field of ophthalmology have been discussed. An attempt has been made to indicate that "shock" therapy produces lesions which resemble pathologically the ocular lesions attributed to allergy. All these accidents are manifestations of tissue anoxia. All can be the result of varying degrees of arteriolar spasm and increased capillary permeability. Many can be attributed to histamine. Histamine is probably the cause of many ocular and extraocular allergic lesions. Allergic lesions are due to capillary anoxia; the symptoms are due to the resulting tissue anoxia. It does not seem reasonable to treat allergic lesions of the eyes with therapeutic agents which not infrequently cause similar ocular or extraocular lesions in persons previously free of such lesions. As Horder [54] said in 1933 regarding shock therapy, some modern treatments consist in "seeing what can be done by direct action severed from physiological principles."

ACUTE CONGESTIVE GLAUCOMA

During the past fifteen years many clinicians have stated that acute glaucoma can be regarded as a localized intraocular vascular catastrophe. Because epinephrine caused dilatation of the pupil of the sound eye in 12 of 15 cases of unilateral glaucoma, Knapp [55] concluded that susceptibility to epinephrine might be present long before the usual clinical signs of glaucoma were apparent. Gifford [56] stated the opinion that vascular disturbances are important and that the effects of nervous influences on ocular tension are probably mediated by an action on the blood vessels, especially the capillaries. Changes in blood chemistry may alter capillary permability; swelling of the vitreous may be a factor, and low grade "inflammation" may play a part by producing venous stasis or increased capillary permeability or both. Gifford also stated that several factors may play a role in any given case, accounting for the clinical differences among patients and their variable response to treatment.

In 1931 Goldenburg [57] gave the results of a study of 12 cases of congestive glaucoma. Every case presented definite evidence of altera-

54. Horder: Brit. M. J. **1**:859 (May 20) 1933.

55. Knapp, A.: Arch. Ophth. **50**:556, 1921.

56. Gifford, S. R.: The Pathogenesis of Glaucoma, Arch. Ophth. **3**:88 (Jan.) 1930.

57. Goldenburg, M.: Am. J. Ophth. **14**:944 (Sept.) 1931.

tion of the vascular system, such as changes in the capillaries of the skin, increased blood pressure, sclerosis of the larger thoracic vessels, asthma (in 1 case) and hay fever (in 1 case). His conclusion was:

> . . . the inherent cause of glaucoma lies in alterations in the capillaries, particularly of the ciliary body, these alterations consisting of an increase in permeability . . . with a resulting swelling of this body, thus encroaching on the avenues leading to the canal of Schlemm.

In an earlier paper Goldenburg [58] mentioned that this abnormal dilatation and permeability of the uveal capillaries were due to a stimulus which might be toxic, hormonal or nervous.

Friedenwald [59] discussed 11 eyes which had been removed after attacks of acute glaucoma. In the earlier and more acute stages serous, hemorrhagic and fibrinous extravasations were present in the ciliary processes. He attributed the intraocular pathologic process to a capillary poison because immediately after a tension-reducing operation on such an eye massive edema of the conjunctiva often occurs. He found that intracutaneous injection of aqueous from an eye with acute glaucoma into the same patient caused an urticaria-like wheal to form, which increased in diameter from 3 to 7.5 mm. in seventeen minutes. Normal aqueous and saline solutions did not produce similar whealing. He concluded: [59]

> . . . Since no lesions of larger vessels were found, one must conclude that the extravasations and the edema fluid are derived from the capillaries. Since capillary walls are known to be impermeable normally to the protein elements of the blood plasma, the permeability of the capillary walls has been increased. . . . Vasomotor influences cannot . . . be eliminated, but in some cases of acute glaucoma a transportable vasotoxic substance is demonstrably present in the intraocular fluids. Whether this is the cause or the result of the glaucoma cannot at present be determined.

Friedenwald and Pierce [60] also reported that injection of histamine into the vitreous of animal eyes caused a prompt and prolonged rise in tension, followed by a fall to below normal. When histamine was injected into the anterior chamber, there was a rise in tension of short duration, a fall and then a second rise to normal or above normal, and there was also edema of the cornea and conjunctiva. They noted that when different animals of the same species were given the same dose of histamine under conditions as nearly identical as possible pro-

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58. Goldenburg, M.: Am. J. Ophth. **11**:290 (April) 1928.

59. Friedenwald, J. S.: The Pathogenesis of Acute Glaucoma: I. Clinical and Pathologic Study, Arch. Ophth. **3**:560 (May) 1930.

60. Friedenwald, J. S., and Pierce, H. F.: The Pathogenesis of Acute Glaucoma: II. Experimental Study, Arch. Ophth. **3**:574 (May) 1930.

found variations in the degree of reaction were observed. This last fact, I believe, speaks for a variation in hypersensitivity to histamine.

In my opinion, the sudden release at operation of aqueous containing histamine or a histamine-like substance explains the not uncommon development of acute glaucoma in the second eye shortly after operation on the first eye. In these cases the arterioles and capillaries are hypersensitive to histamine, and the vessels in the ciliary body are more sensitive than those in other tissues of the body. It is not unlikely that acute glaucoma and acute cyclitis are closely related. Glaucoma, however, is a capillary rather than an arteriolar disease. Because it often occurs in persons of the older age group, the arterioles, having thickened walls, cannot go into complete spasm. Acute glaucoma represents prestasis and/or stasis. Cyclitis and iridocyclitis are due to both arteriolar spasm and increased capillary permeability. These are manifestations of peristasis, or leukostasis. In acute glaucoma the eye is hard and the condition is analogous to an urticarial wheal. Because the arterioles are relatively patent, fluid can reach the capillaries, where it leaks out. In iridocyclitis there is also arteriolar spasm; little or no fluid gets to the capillaries; so it cannot leak out into the ciliary body and aqueous in large quantities, and hypotony occurs. Atropine is of value in the treatment of iridocyclitis; it is also indicated in the postoperative treatment of acute glaucoma. Is this because atropine has the side effect of dilating blood vessels?

My only criticism of the experimental work of Friedenwald and Pierce is that clinical conditions were not duplicated. If histamine is the cause of acute glaucoma, I think that it is formed elsewhere in the body and then transported by the blood to the ciliary body, where it first acts on the capillaries, and possibly the arterioles, causing edema of the ciliary body, and that its occurrence in the aqueous is secondary, not primary. Injection of histamine into the vitreous or the aqueous does not simulate clinical conditions.

In 1933 Duke-Elder [61] stated that a histamine-like substance could explain the rise of intraocular pressure which occurs after one produces total cessation of the intraocular circulation and that this substance was related to the H-substance of Lewis. He noted that axon reflexes, initiated by stroking the iris, caused a rise of tension in animal eyes. Presumably, axon reflexes and antidromic impulses liberate histamine at sensory nerve endings. While I agree with Duke-Elder that histamine can produce hypertension of the eye, I think that stopping the circulation produced intraocular anoxia and that this would suffice to cause increased capillary permeability.

61. Duke-Elder, W. S.: Brit. M. J. **1**:879 (May 20) 1933.

A year later Evans and Evans [62] stated:

> The essential lesion in acute congestive œdema may be said to be an "angioneurotic œdema oculi." This might be more specifically defined as chemiconervous.
>
> Venous stasis appears to be the primary factor, but it may be secondary or at least only contributory to arteriolar contraction and capillary dilatation and increased permeability, due to disturbance of the sympathetic and parasympathetic balance of the innervation of these vessels. A further factor may be the presence in excess of histamine bodies in the capillary area.
>
> . . . the trigger action which results in stasis and capillary transudation is supplied by nervous impulses from the higher centers . . . or from peripheral nerve impulses and antidromic impulses.

They also mentioned that epinephrine may constrict arterioles temporarily but that secondary congestion often follows its use.

After stating that histamine causes both arteriolar constriction and increased capillary permeability, they suggested: [62]

> . . . release of histamine in the tissues . . . is an important exciting factor in the initiation and maintenance of the angioneurotic œdema of the eye which constitutes congestive glaucoma.
>
> Acetyl-choline is the physiological antagonist of adrenalin [and of histamine]. It produces dilatation of arterioles and constriction of capillaries. . . . It is for these reasons that it reduces venous congestion and capillary stasis.

They mentioned the hypothesis, well known today, that physostigmine enhances the effect of acetylcholine by inhibiting the esterase and that the substance causing contraction of the pupil and dilatation of the arterioles may well be not physostigmine itself but acetylcholine, the survival of which it promotes. These authors then reported several cases of acute glaucoma in which more or less temporary benefit was obtained with subconjunctival or intramuscular injections of acetylcholine.

In a more recent article, Evans [63] stated that the causes of acute congestive glaucoma are those of capillary and venous stasis and that the ocular changes are due to a disturbance of the local circulation. Decompensation of the production of aqueous or its removal from the eye is the only feature common to a number of distinct conditions. He also located the essential pathologic process in the capillaries and venules. Emotional instability at the menopause or later and the action of hormones on blood vessels are also factors. Arteriosclerosis probably plays a role. The factors involved may be central or blood borne, as in the case of hormones, "toxins," vitamins and histamine. Closure of the filtration angle is a secondary result of glaucoma, but an important complication.

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62. Evans, J. J., and Evans, P. J.: Tr. Ophth. Soc. U. Kingdom **54**:527, 1934.
63. Evans, P. J.: Brit. J. Ophth. **23**:745 (Dec.) 1939.

Weinstein [64] could find no relation between hypertension and glaucoma. He agreed with Müller and Parrisius, who showed by capillarioscopy that the vasomotor instability of glaucomatous patients is a characteristic peculiarity. Moreover, he stated that the acute capillary dilatation observed during attacks of glaucoma is possible only with an elastic vessel wall, and not with the rigid, brittle walls of arteriosclerosis. He noted that of 3,254 glaucomatous patients 60 per cent were women and that 80 per cent of the acute attacks occurred in women at the time of the climacteric. Because of the preponderance of cases in women, Weinstein expressed the belief that an endocrine factor is important. During the climacteric there is vasomotor instability, as shown by "congestion," perspiration and other vasomotor reactions.

He also mentioned the relation of glaucomatous attacks to cold weather and noted that this indicates vasomotor instability of the capillaries. Brückner [65] had commented earlier on this well known relationship, mentioned in 1902 by Steindorff, who said that cooling of the body produced a disturbance in blood flow. Brückner stated that sensitiveness to weather is an individual insufficiency which tends to increase with age. The work of Horton, Brown and Roth,[66] who proved that hypersensitivity to cold is due to histamine produced in the skin and carried by the blood to other parts of the body, would seem to indicate that histamine is the responsible agent in cases of acute glaucoma associated with chilling of the face or body.

Luedde [67] recently said that glaucoma is an intraocular edema with inadequate drainage and may be caused by general or local conditions which influence capillary permeability or obstruct the drainage of aqueous. He stated that capillary permeability may be affected by vasomotor disorders related to nervous or chemical stimuli, to posture or to trauma, as well as by toxic or nutritional alterations of the blood plasma, which may alter the intracapillary colloid osmotic pressure of the blood.

Kirwan,[68] in reporting on glaucoma in cases of epidemic dropsy, noted that the dropsy was due to eating rice which contained a toxin apparently formed by a spore-forming, gram-positive proteolytic bacillus of the vulgatus group, which is commonly found in diseased rice. The bacillus was found in the urine and stools of a number of patients. This

64. Weinstein, P.: Brit. M. J. **1**:436 (March 4) 1939.

65. Brückner, A.: Physiologic and Clinical Ophthalmologic Problems in Relation to Individual Variability, Arch. Ophth. **20**:912 (Dec.) 1938.

66. Horton, B. T.; Brown, G. E., and Roth, G. M.: Hypersensitiveness to Cold. J. A. M. A. **107**:1263 (Oct. 17) 1936.

67. Luedde, W. H.: Am. J. Ophth. **23**:388 (April) 1940.

68. Kirwan, E. W. O'G.: Primary Glaucoma—A Symptom of Epidemic Dropsy, Arch. Ophth. **12**:1 (July) 1934.

toxin is "soluble in water, resembles histamine and causes a 'cardio-capillary crisis.'" A vitamin deficiency may have been the basic factor. Since all patients with epidemic dropsy do not have glaucoma, Kirwan stated that in some cases "the toxins showed a special predilection for the intraocular endothelium."

Later, Kirwan and Mukerjee [69] assumed that a toxic agent in the plasma produced the capillary dilatation and increased capillary permeability of glaucoma associated with epidemic dropsy. They referred to Chopra and De, who found a histamine-like base in the blood in cases of epidemic dropsy.

Also, Ridley [70] noted that Ryecroft, in 1934, found a vasotoxic substance in the aqueous in 3 out of 4 cases of acute glaucoma. Ridley stated that this substance resembled histamine.

Kraupa [71] reported on a condition he called glaucoma allergicum. This was a serous cyclitis with opacities in the vitreous and keratitic precipitates but without posterior synechias.

Weekers and Barac [72] presented a case which they considered one of Quinicke's edema inside the eye. Both eyes were lost. They suggested the term "paroxysmal intraocular edema" to differentiate the condition from cyclitis and other forms of glaucoma. They referred to Kraupa's case and mentioned a case of Bailliart's in which there was edema of the conjunctiva that underwent variations parallel to those of the glaucoma.

Schroeder [73] explained the various stages of glaucoma on the basis of nutritional edema. He expressed the belief that the active stage of acute glaucoma is an angioneurotic edema of the eye. Among probable etiologic factors he includes protein deficiency, faulty assimilation, anemias resulting from infection, nutritional disturbances and hemorrhage, and possibly B avitaminosis.

Schoenberg [74] stated that acute glaucoma could be due either to a failing parasympathetic or to an overactive sympathetic nervous system or to a combination of the two. In cases of acute glaucoma associated with emotional upsets which he [75] reported the condition probably was due either to sympathetic overaction or to large amounts of epinephrine in the blood stream. Moon,[26] however, stated that the effect of large doses of epinephrine is similar to that of histamine in that the prolonged

69. Kirwan, E. W. O'G., and Mukerjee, S. N.: Brit. J. Ophth. **22**:329 (June) 1938.

70. Ridley, F.: Tr. Ophth. Soc. U. Kingdom **58**:590, 1938.

71. Kraupa, E.: Arch. f. Augenh. **109**:416 (Dec.) 1935.

72. Weekers, L., and Barac, G.: Arch. d'opht. **1**:193 (March) 1937.

73. Schroeder, H.: New Orleans M. & S. J. **87**:671 (April) 1935.

74. Schoenberg, M.: Brit. J. Ophth. **22**:417 (July) 1938.

75. Schoenberg, M. J.: Role of States of Anxiety in the Pathogenesis of Primary Glaucoma, Arch. Ophth. **23**:76 (Jan.) 1940.

vasoconstriction causes capillary anoxia with increased capillary dilatation and permeability.

Therapy.—Besides physostigmine, pilocarpine and acetylcholine, other drugs have been used for acute glaucoma. Thiel and Heim instituted the use of ergotamine tartrate, which probably acts by paralyzing the motor endings of the sympathetic nervous system. Josephson [76] reported good results with adrenal cortex extract. This is presumed to act by regulating salt metabolism and decreasing capillary permeability. Woods [77] could not confirm Josephson's work. Hamburger, Gifford and others have used epinephrine. Hypertonic solutions of dextrose or sucrose have been recommended by other workers. Paul,[78] and later Miller,[79] used splenic extract because Paul considered that acute glaucoma was a manifestation of allergy and because splenic extract had been helpful in some cases of urticaria. Clarke [80] used mecholyl and neostigmine, which act similarly to acetylcholine and physostigmine.

Rabinowitch [81] tried a totally different type of therapy. Instead of using drugs which act on the sympathetic or the parasympathetic nervous system, he used amyl nitrite, which acts directly on the arteriolar walls and is a vasodilator. He reported 16 cases of glaucoma (9 of acute inflammatory glaucoma, 3 of chronic inflammatory glaucoma and 4 of simple glaucoma); with inhalations of amyl nitrite 13 patients showed improvement. The patients with acute inflammatory glaucoma responded best, and those with simple glaucoma showed no response. Because the action on the tension was not permanent, Rabinowitch recommended amyl nitrite only for interrupting the attack.

From a brief consideration of these few recent articles, it is apparent that the idea of acute glaucoma being primarily due to capillary dysfunction has been slowly developing. Many investigators consider it to be an angioneurotic edema. Many have implicated histamine or histamine-like bodies as the etiologic agent. Others prefer the theory of an autonomic imbalance. Changes in weather seem to play a role, but histamine accounts for the glaucoma in these cases. Endocrine influences also probably act via the arterioles and capillaries by raising or lowering the threshold of response to vasomotor stimuli. If protein

76. Josephson, E. M.: Eye, Ear, Nose & Throat Monthly **13**:453 (Jan.) 1935.

77. Woods, A. C.: The Use of an Extract of Adrenal Cortex in Glaucoma, Arch. Ophth. **14**:937 (Dec.) 1935.

78. Paul, T. M.: Urol. & Cut. Rev. **38**:207 (March) 1934.

79. Miller, E. A.: Am. J. Ophth. **22**:536 (May) 1939.

80. Clarke, S. T.: Am. J. Ophth. **22**:249 (March) 1939.

81. Rabinowitch, M. G.: Sovet. vestnik oftal. **7**:181, 1935; abstracted, Arch. Ophth. **15**:936 (May) 1936.

allergy is the cause, the antigen-antibody reaction liberates histamine or a histamine-like body. Lack of the vitamin B complex means lack of nicotinic acid, a vasodilator, and lack of thiamine, which is said to potentiate the action of acetylcholine by neutralizing esterase.

Since allergy is a manifestation of altered permeability of membranes or of smooth muscle spasm, it is obvious that acute congestive glaucoma can also be considered allergic. All substances, whether of chemical, nervous or endocrine origin, which, by virtue of their presence or their absence, alter capillary permeability or cause arteriolar spasm are possible etiologic agents. Since oxygen is most important for maintaining normal capillary permeability, and since ordinarily the blood contains sufficient oxygen, it is apparent that acute glaucoma is a manifestation of localized capillary and tissue anoxia.

Two factors operate to produce glaucoma: first humoral or nervous influences, which act like histamine in causing either arteriolar spasm or increased capillary permeability or both, and, second, hypersensitivity of the vascular system of the ciliary body to these influences. The rise in tension is a secondary effect, depending on a number of variables, such as size and position of the lens, the effect of a dilated pupil on the filtration angle and, probably, the rate at which the leaking capillaries allow fluid to pass into the ciliary body.

In all cases glaucoma can be regarded as due to failure of homeostasis; but not in all cases is the condition due to the same etiologic agent, and in many cases several etiologic factors are concerned.

Furthermore, all drugs which seem to be of value in lowering the tension act directly on arterioles. Most of them also act on the sphincter iridis. In the past it has been assumed, perhaps wrongly, that the pupillary responses were of major importance. For that reason, the reports of Evans and Evans and of Rabinowitch are of fundamental interest. Amyl nitrite acts only on arterioles. Moreover, as Pickering [80] reported, amyl nitrite quickly abolishes the headache which results from the intravenous injection of histamine. In addition, Drinker and Bronfenner,[82] cited by Seegal reported that amyl nitrite caused relaxation of the constriction of the pulmonary vessels which occurs in the rabbit in anaphylactic shock, and they concluded that the arterioles were the site of the spasm. Since anaphylactic shock is assumed by many workers to be due to histamine, it is apparent that glaucoma can be a manifestation of allergy, since a histamine origin explains many cases. In those cases in which the glaucoma is not attributable to histamine, other factors affecting the arterioles or capillaries can be blamed as etiologic agents. All drugs which relieve glaucoma also have arteriole-dilating properties. Amyl nitrite has a dilating action

82. Drinker and Bronfenner, cited by Seegal.[16]

on the arterioles; yet it is effective in temporarily relieving acute glaucoma, in aborting histamine headache and in relieving some of the effects of anaphylactic shock. The pathology of histamine is the pathology of allergy, and both agents cause capillary and tissue anoxia. The physiologic antagonists of histamine are the physiologic antagonists of allergy, and all these physiologic antagonists relieve tissue anoxia by improving the supply of oxygen-containing blood to the anoxic tissues. Which cases of acute glaucoma are due to protein allergy (histamine resulting from antigen-antibody reaction) and which to physical allergy (histamine formed by action of cold on the skin) or to overaction of the sympathetic nervous system cannot always be determined. Whatever may be the cause of acute glaucoma, the disease is a manifestation of capillary and tissue anoxia. Meyer and Cook [83] have stated that defective tissue oxygenation is often merely a final common pathway of etiologically different disease processes.

HERPES

The various types of herpes of the cornea, as well as herpes zoster ophthalmicus, can be attributed to a lesion in the gasserian ganglion. In cases of dendritic keratitis, such a lesion accounts for the diminished corneal sensitivity, as well as the intense pain and headache, both of which are out of proportion to the extent of the corneal lesion.

Moore,[84] in discussing herpes zoster ophthalmicus, said:

> . . . If the patient has died with the eruption still out upon the skin, the affected ganglion will be found to be in a condition of profound inflammation, with areas of extravasated blood; or if the patient has died quite early, the blood may be seen with the naked eye. Similar changes are present in that part of the sheath which covers the diseased portion of the ganglion; the vessels are engorged, blood is extravasated, and the sheath is invaded by multitudes of small round, deeply staining cells. As soon as the inflammation has expended itself absorption begins, and ultimately the focus becomes converted into fibrous tissue; within this area all ganglion cells and nerve fibers are destroyed and the overlying sheath is thickened.

Paton [85] mentioned the same changes, his description being based on Head and Campbell's report in 1900. These herpetic lesions have been attributed to a virus, to allergy, to foci of infection and to toxemia. The pathologic process is the same as that of anterior poliomyelitis, but sensory rather than motor nerve cells are involved. Paton mentioned that the corneal and cutaneous lesions have been attributed to interference with trophic nerve fibers and to vasomotor changes.

Many physiologists have mentioned that "irritation" of the posterior root ganglions sets up antidromic impulses which cause the peripheral

83. Meyer, A., and Cook, L. C.: J. Ment. Sc. **83**:258 (May) 1937.

84. Moore, R. F.: Medical Ophthalmology, ed. 2, London, J. & A. Churchill, 1925.

85. Paton, L.: Brit. J. Ophth. **10**:305 (June) 1926.

cutaneous lesions of herpes zoster. If one agrees that antidromic impulses release H substance or histamine, one has an explanation for the peripheral lesions. What causes the primary changes in the ganglion?

The pathologic changes in the ganglion are basically similar to those of episcleritis, retrobulbar neuritis and closure of the central retinal artery. There are edema, round cell infiltration, extravasations of red blood cells and capillary dilatation. In other words, varying degrees of prestasis, peristasis and stasis occur. This is the pathology of allergy. The fact that the gasserian ganglion is concerned with relaying sensory impulses centrally accounts for the pain in the eye, headache, disturbances in the skin and corneal sensitivity. The fibrous sheath of the ganglion prevents any expansion of the edematous tissue; so pain is outstanding, even when only the sensory fibers to the cornea are involved. Herpes of the cornea and herpes zoster ophthalmicus differ probably only in the location and size of the lesion in the ganglion.

The factors predisposing to herpes are similar to those for other allergic lesions of the eye. Among these factors are head colds, infections of the upper respiratory tract, exposure to cold, "toxemia" and a sudden change in the meteorologic environment.

In my opinion, the changes in the ganglion are manifestations of tissue anoxia. Herpes due to cold and allergy is as likely to be due to histamine as are choroiditis, retrobulbar neuritis and scleritis. Herpes is analogous to acute glaucoma except that the one involves the eye whereas the other involves a ganglion. Both can be considered as manifestations of an angioneurotic edema.

Capillary permeability is increased in association with herpes. This change may be due either to arteriolar spasm or to primary changes in the capillary endothelium. Either histamine or a histamine-like body can account for these vascular changes in the ganglion. Either the increased intraganglionic pressure or the tissue anoxia or both in some way initiate antidromic impulses which cause the cutaneous and ocular lesions. Such a conception of the herpetic lesion provides for a self-perpetuating mechanism due to a nonliving chemical substance. Histamine produced anywhere in the body acts on the gasserian ganglion. Antidromic impulses are initiated which liberate H-substance (histamine?) and cause the distant cutaneous and ocular lesions. The histamine liberated peripherally not only accounts for the peripheral lesions but may be absorbed and either intensify and continue the process in the ganglion or cause vascular lesions in any other tissue of the body where there are histamine-sensitive cells. Such an interpretation adequately explains lesions attributed to viruses as manifestations of disordered physiologic functions.

Four cases are reported briefly in which only therapy directed toward relieving the localized tissue anoxia was used. In other cases similar treatment has met with equally good results, but these 4 instances will suffice to indicate the value of vasodilator therapy for herpes.

CASE 1.—Mrs. R. R., a woman aged 34, was seen on Dec. 20, 1939, with severe herpes zoster ophthalmicus involving the left side of the forehead. There was also one vesicle on the left upper lid; this lid was extremely edematous. The lesions had been present for five days. The pain was unbearable and had not been relieved with sedatives and local applications to the skin. The left eye, which was normal, was not affected.

The only cause ascertainable was exposure to cold. On December 13, after having her hair washed, she had gone out in the cold and "taken in" a neighbor's washing. She had been thoroughly chilled after this and had experienced great difficulty in getting warm after the exposure.

She was given 0.1 Gm. of sodium nitrite intravenously on December 20, 21, 22 and 23 and 30 mg. of erythrityl tetranitrate twice daily from December 21 to Jan. 5, 1940. On December 21 the pain was less severe; on December 22 there was no pain, the edema of the lid had decreased and she could tolerate firm pressure on the left side of the forehead. On December 23 she had no subjective complaints, and the vesicles had started to regress. They disappeared in about ten days. There have been no recurrences.

CASE 2.—R. S., a girl of 9, was seen on April 1, 1940 with the complaint that the left eye had been red and irritated for eleven days. One week before the eye was involved she had had a head cold.

Vision in the left eye was 20/70—, and the eye was soft. There was pronounced circumcorneal injection. On the cornea there were several superficial, grayish vesicles, which stained at their apexes. The cornea was hazy, and the sensitivity was greatly reduced. The markings of the iris were indistinct, and a few dilated blood vessels could be seen on the iris. The patient complained of severe pain in the eye and headache on the left side. Photophobia was intense. Atropine salve was placed in the conjunctival sac, and the patient was given 70 mg. of sodium nitrite intravenously on April 1, 2, 3 and 6.

Improvement was rapid. On April 2 the pain had disappeared, the ocular tension had improved, the circumcorneal injection was less noticeable and corneal sensation had improved. On April 6 the eye was nearly white. On April 10 vision was 20/20, the eye was completely white, corneal sensation was normal and the corneal lesions were represented by tiny subepithelial opacities. There have been no recurrences.

This case was one of herpes corneae with mild herpetic iritis. Vasodilators caused immediate relief of the symptoms, and the ocular lesions regressed rapidly. Because of the photophobia, this patient received atropine for six days.

CASE 3.—R. M., a man of 23, was seen on May 7, 1940. He complained of tearing and photophobia in the right eye with severe pain in and behind that eye. He had spent May 5 in a mountain camp, where it had been very cold in the evening. On May 6 the aforementioned symptoms developed, and there were also symptoms of a mild "head cold."

Vision in the right eye was 20/25—. Photophobia and tearing were pronounced. There was moderate circumcorneal injection; the corneal sensitivity was reduced, and in the pupillary region of the cornea there were three elevated, grayish lesions, which did not stain. The iris was greenish; its markings were blurred, and there were a few cells in the anterior chamber. The left eye was amblyopic.

This patient received 0.1 Gm. of sodium nitrite intravenously on May 7, 8, 9, 10 and 11, and 30 mg. of erythrityl tetranitrate each evening from May 7 to May 13. A drop of scopolamine hydrobromide was instilled in the conjunctival sac on May 7, 8 and 9. The eye was not covered with a patch.

On May 8 the photophobia, tearing and redness were less intense. On May 9 the aqueous was free of cells, and the iris was less greenish. There was still a faint circumcorneal injection. The patient had no subjective complaints. On May 11 the eye was completely white. One tiny gray opacity was present in the pupillary region of the cornea; this opacity was definitely subepithelial. There have been no recurrences to date.

In this case, which was similar to case 2, cure occurred in four days after intensive vasodilator therapy, which was directed toward the lesion in the gasserian ganglion rather than toward the secondarily involved cornea and iris.

CASE 4.—J. H. S., a man of 47, was seen on Jan. 15, 1944. On or about Jan. 1, 1944 herpes zoster ophthalmicus developed on the left side. On January 11 the left eye became painful, vision was foggy and there was lacrimation.

On examination (January 15) he had one herpetic vesicle at the hair line on the forehead, three on the left side of the forehead, one on the left side of the nose and one on the columella of the nose. There was moderate pain in the affected region.

Vision in the left eye was 20/70— and was not improved with any lens. There was a faint circumcorneal injection, and the whole cornea had a whitish, pebbly appearance, due to deep keratitis. After dilation of the pupil a faint red reflex was obtained, but no details of the iris, optic nerve or retinal vessels could be observed. The field was grossly normal. The right eye was entirely normal.

Treatment consisted in administration of 100 mg. of nicotinic acid three times a day after meals, 30 mg. of erythrityl tetranitrate on retiring and 1 drop of 0.25 per cent scopolamine hydrobromide in the left eye twice daily.

On January 18 the cornea was clearer, so that it was possible to see deposits on its posterior surface. The pupil was in mid-dilation, and the iris was greenish. There were no synechias. There was a decrease in the pain in the region of the vesicles on the face.

On January 22 vision was 20/40 and the cornea was much clearer so that the deposits on the posterior surface of the cornea were clearly visible. The patient stated that improvement in vision had occurred on January 20 and that he was free of all pain.

On January 28 vision was 20/25 + 2, the eye was white, the depositis on the cornea were fewer, the media were clear and the fundus was normal. At this time the patient was pronounced clinically cured because he was entirely free of symptoms and the vesicles on the face had disappeared almost entirely.

He continued to take nicotinic acid by mouth for three weeks longer. On February 4 and February 18 vision was 20/16 — 3 and there were still deposits on the back of the cornea.

He was last seen on Nov. 20, 1944. At this time vision was 20/16 — 2. The left pupil was slightly larger than the right, and there was some atrophy of the superior pupillary margin of the iris. The deposits on the posterior surface of the cornea had entirely disappeared.

This was a case of herpes zoster ophthalmicus with keratitis profunda and cyclitis. The most likely etiologic factor was exposure to cold weather. A clinical cure was obtained in thirteen days with the administration of vasodilators by mouth.

In my opinion, herpes zoster ophthalmicus, herpes corneae and herpes iridis are not diseases *sui generis* but are basically the same as other allergic lesions except that the primary pathologic process is located in the gasserian ganglion. A histamine origin accounts for both the central and the peripheral lesions. Whether the histamine is derived from the skin, an antigen-antibody reaction or a virus (?) cannot be determined. The development of herpes in 46.2 per cent of the 411 patients treated with artificial fever by Warren, Carpenter and Boak [47] offers much evidence for a histamine origin of herpes. Since the heating of tissues, as well as the cooling, results in the formation of histamine, there is no necessity for assuming that these ocular lesions are due to a virus. The various herpetic lesions of the eye are due to an acute vascular catastrophe in the gasserian ganglion. The pathology is that of allergy and also that of histamine poisoning. Therapy directed toward the assumed vascular changes (arteriolar spasm and increased capillary permeability) seems to be more effective than the customary methods. Such therapy, which acts by increasing the supply of oxygen-containing blood and thereby relieving the capillary and tissue anoxia, is based on physiologic principles and deserves a trial in similar cases.

PARALYSIS OF OCULAR MUSCLES

Appelbaum [2] referred to a case of Lemoine's in which the patient had attacks of diplopia, vertigo and scintillating scotoma without headache. Allergy to cheese was considered the cause because the attacks ceased after the patient eliminated cheese from his diet.

Kahoun [86] reported 8 cases of paralysis of one or more of the ocular muscles following influenza. In 1 case at the beginning of the influenza, all the muscles of the right eye became paralyzed, and this condition did not improve. Of the 7 remaining cases in which paralysis developed during convalescence and ran a benign course, bilateral perineuritis was present in 1 and typical retrobulbar neuritis in another.

Since many of the manifestations of influenza are due to diffuse, but mild, changes in the function of the arterioles and capillaries, and

86. Kahoun, S.: Ceskoslov. oftal. **3**:109, 1937; abstracted, Am. J. Ophth. **21**:458 (April) 1938.

since influenza is considered to be a manifestation of allergy, it is apparent that Kahoun's cases represented instances of allergy with focal areas of edema in the oculomotor nerves or in the oculomotor nuclei, as well as in the optic nerves. Had the optic and retrobulbar neuritis been accompanied with symptoms referable to the spinal cord, the diagnosis of neuromyelitis optica could have been made. Neuromyelitis optica often follows an infection of the upper respiratory tract or influenza. When it does not, it is considered to be acute multiple sclerosis by some authorities.

Many patients with influenza complain of pains in the muscle and of muscular weakness. Possibly these are preclinical states of neuromyelitis optica. Moreover, the pathology of neuromyelitis consist in localized areas of softening and necrosis with perivascular lymphocytic infiltration. This is the pathology of allergy, and this is the stage which Ricker and Krogh would characterize as peristasis, or leukostasis. It is also the pathology of acute retrobulbar neuritis.

If multiple sclerosis is due to allergy, as suggested by Kennedy [87] and many others, or if it is a primary vascular disease, as asserted by Oppenheim [88] in his textbook many years ago, all the manifestations of this disease are of either allergic or vascular origin. If vascular, they may be manifestations of allergy. In many cases of paralysis of isolated extraocular muscles the cause may be angiospasm. These cases may be examples of monosymptomatic multiple sclerosis.

Kennedy, Wortis and Wortis [89] also noted that vascular accidents occur in the brain in cases of untreated syphilis, and they attributed such accidents to angiospasm.

Assuming that the various types of paresis of ocular muscles may be allergic and due to angiospasm, with resulting capillary and tissue anoxia, I wish to report 7 cases in which only vasodilators were employed. Whether the pathologic process was located in the nerves or the nerve centers could not be determined. It was probably not located in the muscle substance itself.

Case 1.—R. N., a man of 60, was seen on Aug. 29, 1938 with paresis of the right internal rectus muscle, of two days' duration. He could adduct the right eye 30 degrees to the left. On September 9, after eight intravenous injections of sodium nitrite (0.1 Gm.) and oral administration of erythrityl tetranitrate, he was free from symptoms and could adduct the right eye 60 degrees to the left without the occurrence of diplopia. The Wassermann reaction of the blood was strongly positive; so he was referred for antisyphilitic treatment, after partial paralysis of the third nerve was cured.

87. Kennedy, F.: New York State J. Med. **36**:469 (April 1) 1936.

88. Oppenheim, H.: Diseases of the Nervous System, translated by E. E. Mayer from the second German edition, Philadelphia, J. B. Lippincott & Co., 1900.

89. Kennedy, F.; Wortis, S. B., and Wortis, H.: New York State J. Med. **38**:1441 (Nov. 15) 1938.

CASE 2.—M. B., a Negro of 42, was seen on Nov. 14, 1938 with the complaint of double vision, present for ten days. He had almost complete paralysis of the left external rectus muscle and could abduct the left eye only 10 degrees beyond the midline. He received nine daily injections of sodium nitrite. On November 18 he could abduct the left eye 40 degrees beyond the midline; with both eyes open, diplopia did not occur until he rotated his eyes 50 degrees to the left. On November 23 he could abduct the left eye 60 degrees beyond the midline. The Wasserman reaction of the blood was 4 plus. He began to receive antisyphilitic treatment on November 18, at which time he had recovered at least 50 per cent of the lost function of the external rectus muscle.

CASE 3.—J. K., a man of 68, was seen on Jan. 24, 1938 with paralysis of the left external rectus muscle, present for twenty-three days. The left eye could not be abducted beyond the midline. He received nine daily intravenous injections of sodium nitrite (0.1 Gm.). He could abduct the left eye 30 degrees beyond the midline on February 2, 40 degrees on February 18, 50 degrees on March 11 and 60 degrees on March 18. At the last visit he had only a trace of diplopia in gazing to the extreme left. This patient's improvement began coincidentally with the institution of vasodilator therapy. Fifty-three days after treatment was started he had recovered normal function.

CASE 4.—B. W., a man of 45, was seen on Aug. 14, 1937 with complete paralysis of the left external rectus muscle, present for five days. After twenty daily intravenous injections of sodium nitrite (0.1 Gm.) he could abduct the left eye normally without diplopia. The Wassermann reaction of the blood was negative.

CASE 5.—S. S., a woman of 25, with advanced multiple sclerosis, nystagmus and bilateral temporal optic nerve atrophy, had onset of paralysis of the elevators of both eyes on May 28, 1938. She received twelve daily intravenous injections of sodium nitrite. Twenty days after the onset of the attack she could elevate her eyes normally. The nystagmus was unchanged.

CASE 6.—J. D., a man of 34, was seen on Nov. 16, 1938 with paresis of the left external rectus muscle, present for several days. He could abduct the left eye 25 degrees beyond the midline with difficulty and had diplopia in the whole field of that eye. On November 28, after ten intravenous injections of sodium nitrite, he could abduct the left eye 45 degrees; diplopia began before this point was reached. He failed to return for further treatment.

CASE 7.—H. M., a man of 30, was seen on Oct. 18, 1937 with paresis of the left external rectus muscle, present for ten days. At the onset he had a head cold. Diplopia occurred when the left eye was abducted 20 degrees. After four daily intravenous injections of sodium nitrite, he could abduct the left eye 30 degrees before diplopia occurred. He stated that he was much better. Because the Wassermann reaction was strongly positive, he was referred elsewhere for treatment. He did not return. This patient showed improvement, and vasodilator therapy should have been continued, as it was in case 1.

Of necessity, controls are difficult to obtain. In 1933 Agatston [90] reported 4 cases of paralysis of the external ocular muscles. Treatment consisted of injections of a bismuth compound, administration of mercury and potassium iodide by mouth and weekly catharsis. The Wassermann reaction was negative in all cases. The patients' ages

90. Agatston, S. A.: M. J. & Rec. **138**:41 (July 19) 1933.

were 50, 38, 59 and 73 respectively; all were men. The muscles involved were, respectively, the internal rectus, the superior oblique, the superior oblique and all muscles supplied by the third nerve. The patients were completely cured in three, six, six and three months, respectively. The third patient (aged 59) later had complete paralysis of the third nerve; with the aforementioned treatment he was cured in thirteen weeks.

The times required for cure in the first 5 of my cases were eleven, nine, fifty-three, twenty and twenty days, respectively. In the other 2 cases improvement occurred, but the patients did not remain under observation and treatment sufficiently long for therapy to be considered either a success or a failure. Dr. Michael Goldenburg has informed me that a patient with paresis of the sixth nerve responded to this treatment.

Agatston used mercury and bismuth preparations and iodides because the ocular muscles are often paralyzed in cases of syphilis and these drugs help to cure the syphilis and the ocular paralyses. I used vasodilators because I believe many of these paralyses are of vascular origin, whether due to allergy, syphilis or other factors. The times of cure were much shorter for the patients treated with vasodilators than for those treated with mercury, bismuth and iodides. In my opinion, the time required for cure must be considered in attempting to evaluate the results of therapy.

RETINA

Serum sickness is considered a manifestation of allergy or anaphylaxis. Over fifteen years ago Brown,[44] in discussing serum sickness in man, said:

> The lesions and reactions in all species are probably fundamentally produced by the same mechanisms, and differ by reason of the difference in anatomic structure and physiologic reactions. Thus, no one symptom or group can be said to be characteristic in all animals. There is one manifestation, however, that can be considered as an accompaniment in all instances of anaphylaxis of which serum sickness is a phenomenon, and that is *vascular dilatation with serous exudation.*

He stated that in serum sickness the initial rise in blood pressure may be due to vasoconstriction, which is followed by paresis and a fall in blood pressure. Then other signs of vasodilatation appear. "Hyperemia" with serous exudation and resulting edema is the most frequent and is, according to the organ or organs involved, the cause of most of the symptoms.

Brown also noted that the fundus presents for inspection a vascular tissue, which is represented by the choroidal vessels, the ciliary system and the retinal system; the disk presents nonmedullated nerve fibers.

Therefore one can study at close range fundamental processes, such as vascular changes associated with nervous manifestations, in vivo.

Brown reported the ocular reactions of 75 patients who received diphtheria antitoxin intravenously. Lacrimation and dilatation of the conjunctival vessels occurred frequently. Changes in the fundus included hyperemia of the disk and retina with elevation of the optic cup. The retinal veins and capillaries were dilated and definite papilledema developed in 20 per cent of cases. There was also a "watered-silk" appearance of the retina in the patients with the severer reactions. About 10 per cent of the patients complained of "blurriness" of vision. Administration of epinephrine had a very temporary effect on the ocular manifestations. The ocular changes cleared up in from four to twenty-eight hours. Experiments on 4 animals resulted in similar changes in the conjunctiva and fundus.

Brown concluded his article as follows:[44]

> The vascular manifestations are perhaps the most striking and the most important concerned. . . . Hyperemia, then, must not be construed to indicate beginning inflammation of the disc, but a marked vasodilatation dependent on the serum reaction.
>
> The direct action of the serum itself, as brought to the tissues, probably does not enter primarily into the ocular reaction. The primary response is a vascular one.

In Brown's cases, capillary dilatation and increased capillary permeability with resulting edema were the outstanding changes. He did not mention the retinal arteries except to say that in a few cases they showed increased tortuosity. Also, exudation from the choriocapillaris may have occurred.

Spastic closure of the central retinal artery or of one of its branches probably represents an allergic reaction in its simplest form, since the present study is concerned anatomically with only vascular and nerve tissue. There is a minimum of connective tissue, and the branches of the retinal artery are practically on the retina. The main trunk, the superior or inferior division or, finally, the nasal or temporal branch of either division may be affected; with involvement of each vessel the fundus picture is characteristic. The loss of function corresponds with the extent of vascular involvement. This is particularly true when only a cilioretinal artery is affected.

Kyrieleis[91] recently pointed out that the term "peristasis" was introduced by Ricker, who applied it to a functional process in the vascular system in which the capillaries were dilated and the arterioles contracted. Kyrieleis reported 3 cases of incomplete arteriosclerotic occlusion of the central retinal artery. Owing partly to organic and

91. Kyrieleis, W.: "Peristatic" Conditions Associated with Incomplete Occlusion of the Central Artery, Arch. Ophth. **23**:447 (Feb.) 1940.

partly to functional causes, a circumscribed narrowing of the arteriole was produced, and in the area supplied by the affected artery there was a circumscribed edematous swelling of the retina. In 1 case hemorrhages developed. Kyrieleis concluded that peristatic circulatory disturbances lead to extravasation of fluid and cellular constituents of the blood through the vessel walls and that the increased capillary permeability is caused by impaired nutrition.

In discussing Kyrieleis' report, Scheerer stated that peristatic hyperemia in cases of occlusion of the central retinal artery is more pronounced when there is no arteriosclerosis. Mylius then stated that he had observed in patients with eclampsia that peristatic conditions preceded the retinal changes.

Marucci [92] reported a case of bilateral retinal angiospasm in a woman of 38 who had been lactating for seven months. She also had nausea and dizziness and had increased in weight for several years. The capillary circulation in the nail beds was definitely pathologic. Acetylcholine and the use of an estrogenic preparation effected complete return of vision to normal. Marucci attributed not only the ocular signs but also the headache and vertigo to vascular spasm. He expressed the belief that ovarian dysfunction was the primary cause of the condition.

Geserick [93] reported the case of a man who from the age of 21 had had repeated intraocular hemorrhages. At 41 he had bilateral atrophy of the optic nerve. The threadlike retinal arteries were in part converted into white lines; the veins were attenuated, and there were chorioretinal lesions close to the vessels. There was no pulse in either dorsalis pedis artery, and neurologic examination led to a diagnosis of disseminated sclerosis. All the changes were attributed to endangiitis obliterans.

This case was one of multiple sclerosis with repeated spasms of the retinal arteries rather than of the vessels supplying the optic nerve. The chorioretinal lesions were also probably due to local circulatory impairment. Whether the vascular spasms were due to allergic, nervous or climatic factors could not be determined from the report.

Bender [94] mentioned the case of a woman who had blurring of vision and diplopia within twenty-four hours after the extraction of four teeth. After thirty-six hours vision was reduced to 1/200 in the right eye; the left eye was totally blind. Clinically, the fundus picture was that of thrombosis of the central retinal vein. After six weeks both nerve heads were white and indistinct and the blood vessels

92. Marucci, L.: Ann. di ottal. e clin. ocul. **64**:671 (Oct.) 1936.

93. Geserick, H.: Arch. f. Ophth. **138**:647, 1938; abstracted, Am. J. Ophth. **21**:1061 (Sept.) 1938.

94. Bender, M. B.: Am. J. Ophth. **18**:148 (Feb.) 1935.

in the fundus were represented by a few whitish streaks radiating from the nerve heads.

This case, in which spastic closure of the central retinal artery must have occurred, is similar to cases of iritis which develops after a focus of infection is opened up or removed. Whether these accidents are due to the flooding of the blood stream with allergins from the focus of infection or to the absorption of blood or to an axon reflex cannot be determined. The fundus picture in Bender's case was that of allergy (peristasis and stasis) and was a manifestation of tissue anoxia.

Toth and Meszaros [95] reported the case of a woman of 70 who on stepping out into the cold air suddenly became blind in the left eye. Later the fundus showed atrophy of the optic nerve and narrowing of the retinal arteries. In the right eye, vision was reduced to 5/15; green was not recognized, and the retinal arteries showed variations in caliber. For four years this patient had noticed that her fingers became white and numb in the cold. The capillaries in the nail beds were scarcely visible and the capillary blood flow was retarded. Vision improved to 5/7 (left eye) after fifteen daily intravenous injections of 10 cc. of a 40 per cent solution of dextrose. In this case the ocular condition can be interpreted either as an allergic reaction to cold or as a pressor vasomotor reflex from the skin. Whatever the cause, exposure to cold was the inciting stimulus, and histamine could have caused the ocular lesions.

Rheumatic fever and chorea are considered manifestations of allergy. Bride [96] reported the case of a girl aged 8 years with chorea, who had closure of the central retinal artery in one eye. When Bride saw her, there was complete atrophy of the optic nerve. If chorea is primarily due to allergy and if closure of the central retinal artery in this patient was a manifestation of rheumatic fever, it is possible that many cases of closure of the retinal artery in young people may represent monosymptomatic rheumatic fever! Moreover, inasmuch as vasodilator drugs are the most effective means of relieving spasm of the central retinal artery, they should be effective in aborting the carditis, arthritis and chorea of rheumatic fever if these conditions also are due to local vascular dysfunction secondary to allergy. I believe that they are.

In some cases detachment of the retina may be of vascular origin and a manifestation of localized anoxia. Several years ago I saw a man who had made many trips by airplane. Thrombosis of the central retinal vein developed in one eye; this cleared up. Later a detachment

95. Toth, Z., and Meszaros, K.: Klin. Monatsbl. f. Augenh. **91**:815 (Dec.) 1933.

96. Bride, T. M.: Tr. Ophth. Soc. U. Kingdom **57**:346, 1937.

of the retina developed in the other eye. Each time he went aloft he became anoxemic. Possibly the thrombosis of the central retinal vein and the detachment were due to localized anoxia secondary to the anoxemia. This viewpoint is not unreasonable, as de Rötth[97] has noted that in cases of detachment a vascular degeneration is usually present. He referred to Vogt's theory that primary damage occurs in the vessels, not in the retina. If anoxemia can cause retinal detachment, then localized tissue anoxia due to arteriolar spasm and increased capillary permeability (which may be due to allergy) can also account for some cases of retinal detachment.

The literature contains many reports of the efficacy of vasodilators in curing spastic closure of the central retinal artery or one of its branches. Minton,[98] Butler, Pickard, Smith and many others have stated their belief that spasm explains the closure in many of these cases. Emboli do occur, as in the case of Orr and Young,[99] but are rare. In sclerosed vessels, which occur in the older age groups, spasm probably precedes a thrombotic occlusion, according to Minton. Tortella[100] stated that the form which responds to vasodilators is due to spasm and that the therapeutic response supplies the necessary data for differential diagnosis.

In conclusion, it is obvious that closure of the central retinal artery can be attributed to cold, stirring up of foci of infection, rheumatic fever, endocrine imbalance, multiple sclerosis and, probably, many other etiologic factors. The changes in the fundus are those of allergy and are attributable to smooth muscle spasm and increased capillary permeability. When allergy is viewed, not as hypersensitivity to allergins but as a vascular response to a number of etiologic factors, it must be apparent that closure of the central retinal artery, particularly in young people, gives the gross picture of allergy. Tissue anoxia results. Treatment directed toward the vascular spasm is the most effective means of treating this manifestation of allergy. Moreover, closure of the central retinal artery is comparable to acute exudative choroiditis, acute iritis and iridocyclitis and acute retrobulbar neuritis.

OPTIC NERVE

The alleged causes of acute optic and retrobulbar neuritis include allergy, focal infection, pregnancy, lactation, endocrine disorders, multiple sclerosis and other demyelinating diseases and serous menin-

97. de Rötth, A.: Bilateral Detachment of the Retina, Arch. Ophth. **22**:809 (Nov.) 1939.

98. Minton, J.: Proc. Roy. Soc. Med. **30**:285 (Jan.) 1937; abstracted, Arch. Ophth. **17**:565 (March) 1937.

99. Orr, H. C., and Young, J. H.: Brit. M. J. **1**:1119 (June 1) 1935.

100. Tortella, L. P.: Arch. de oftal. hispano-am. **34**:544 (Oct.) 1934.

gitis. The condition has followed prophylactic vaccination against rabies [101] and has occurred after combined inoculations against typhoid, cholera and dysentery.[102] Bucy [103] reported a case in which sulfanilamide was the etiologic agent. I have heard of a similar case and have seen a case of bilateral optic neuritis accompanied with unilateral paralysis of the sixth nerve in a boy of 7 who received sulfapyridine. Kahoun [104] reported a case of optic neuritis due to carbon monoxide poisoning; I [105] reported a case in which retrobulbar neuritis and multiple sclerosis occurred in a healthy donor who gave 500 cc. of blood twice within forty-eight hours, and both Moore [84] and Knapp [106] have discussed the occurrence of similar cases following severe hemorrhage.

In many cases optic and retrobulbar neuritis are attributed to sinusitis. A brief survey of the literature revealed 16 authors in favor of and 11 opposed to the theory of a sinus origin for these conditions. Three investigators, Bedell,[107] Campbell [108] and Hoople,[109]

Neuritis, Arch. Ophth. **16**:236 (Aug.) 1936.

favored operation only if there was a purulent sinusitis. Moore [84] was opposed to the theory of a sinus origin, and Benedict [35] expressed the belief that operations on the sinuses act nonspecifically. My opinion agrees with that of the five authorities cited.

Carroll [110] recently stated: "When a cure has been discovered for multiple sclerosis, a cure will have been found for retrobulbar neuritis in many cases." One can say with fully as much logic that when a cure has been discovered for retrobulbar neuritis a cure will have been found for multiple sclerosis in many cases. I believe that symptoms of the latter referable to the spinal cord and those of involvement of the optic nerve are due to a pathologic process of the same type. The location of the lesion determines the symptoms and signs of this

101. Cormack, H. S., and Anderson, L. A. P.: Brit. J. Ophth. **18**:167 (March) 1934. Hasabe: Acta Soc. ophth. jap. **38**:102 (July) 1934. Suzuki: Ibid. **39**:219, 1936.

102. Shannon, C. E. G.: Bitemporal Paracentral Scotoma, Arch. Ophth. **6**:544 (October) 1931.

103. Bucy, P. C.: Toxic Optic Neuritis Resulting from Sulfanilamide, J. A. M. A. **109**:1007 (Sept. 25) 1937.

104. Kahoun, S.: Ceskoslov. oftal. **3**:122, 1937; abstracted, Am. J. Ophth. **21**:340 (March) 1938.

105. Duggan, W. F.: Use of Vasodilators in Treatment of Retrobulbar Neuritis, Arch. Ophth. **16**:380 (Sept.) 1936.

106. Knapp, A.: Medical Ophthalmology, Philadelphia, P. Blakiston's Son & Co., 1918, pp. 407-409.

107. Bedell, A.: New York State J. Med. **33**:361 (March 15) 1933.

108. Campbell, E. H.: Relationship of Sinusitis to Optic and Retrobulbar

109. Hoople, G. D.: New York State J. Med. **33**:365 (March 15) 1933.

110. Carroll, F. D.: Retrobulbar Neuritis: Observations on One Hundred Cases, Arch. Ophth. **24**:44 (July) 1940.

disease. It is probably for this reason that Traquair [111] stated that acute retrobulbar neuritis can be considered a monosymptomatic form of multiple sclerosis.

The pathology of retrobulbar neuritis is the pathology of multiple sclerosis. The pathology of the acute form is presumably the same as the pathology of neuromyelitis optica, first described as a clinical entity by Albutt. Briefly, the optic nerves and other parts of the nervous system show localized areas of softening and necrosis with perivascular infiltration. Ricker would call this stage peristasis, or leukostasis. In cases of the healed form there are sclerotic plaques of glial origin around arterioles whose walls are thickened. Demyelination is a characteristic change. In some instances the arteriolar lumen is obliterated. This is essentially an infarct. Many observers in the past have stated that the glial cells grew and compressed the arterioles and the nerve fibers. Actually, I believe that local circulatory failure causes the myelin to break down and that the glial overgrowth is secondary, not primary.

Many years ago Dawson (quoted by Moore [84]) noted that the sites of predilection for disseminated sclerosis were related to (1) the terminal ramifications of end arteries and (2) areas where much glial tissue is normally present, as in the optic chiasm. Moreover, Kennedy [87] has said that "the recent plaques in the rare autopsies of acute cases [of multiple sclerosis] are not sclerotic; they are infiltrations by fluid of the nerve tissue surrounding blood vessels." Kennedy stated the belief that the episodes, intermissions and curability of the acute crises of disseminated sclerosis "resemble the happenings of localized allergic edemas."

There must be a factor common to all cases of acute retrobulbar neuritis. In analyzing the etiologic factors, it is obvious that in the case of carbon monoxide poisoning the retrobulbar neuritis was due to histotoxic anoxia, caused by loss of ability of the hemoglobin to transport sufficient oxygen to nourish the tissues. The cases following hemorrhage can be ascribed to anemic anoxia. However, when the retina, rather than the optic nerve, is the site of the lesion, one sees not ischemia but edema of the retina with narrowing of one or more of the branches of the central retinal artery. Presumably, the same type of lesion is present in the optic nerve. These lesions can be ascribed to overaction of homeostatic mechanisms which occur after hemorrhage. It is known that after hemorrhage there is a generalized arteriolar constriction, due either to the action of the sympathetic nervous system or to release of epinephrine into the circulating blood or to both factors. This reduces the capacity of the vascular system.

111. Traquair, H. M.: Tr. Ophth. Soc. U. Kingdom **50**:351, 1930.

If this compensatory arteriolar constriction results in excessive spasm, the reactions shift from the zone of normal to that of pathologic physiology. Moon [26] noted that excessive and prolonged arteriolar constriction, such as that produced by overdoses of epinephrine, can produce changes in capillary permeability by so limiting the access of blood to the capillaries that both they and the tissues supplied by them suffer from anoxia. In other words, if posthemorrhagic amaurosis is due to a "toxin," the "toxin" is epinephrine, and it causes amblyopia either of retinal or of retrobulbar origin because of a homeostatic mechanism which is physiologic in nature but pathologic in degree. Also, Landis has frequently reported that lack of oxygen is the most potent factor in causing increased capillary permeability.

In the rare cases of retrobulbar neuritis due to carbon monoxide poisoning and to hemorrhage anoxemia is present. In most of the cases of acute retrobulbar neuritis there is no anoxemia, but I believe that localized anoxia, due to dysfunction of one or two arteriolar capillary units, exists. This dysfunction manifests itself as arteriolar constriction with secondary increased capillary permeability, due to the anoxia resulting from the arteriolar spasm. Allergy, histamine, epinephrine and overaction of the sympathetic nervous system can all cause these arteriolar-capillary changes.

The idea that acute retrobulbar neuritis might be of vascular origin is not new. In 1931 Cross [112] stated that he "thought it possible that some cases of retro-ocular neuritis might be due to a spasm of small vessels going to the nerve-fibres, while others were due to small emboli. Some might be due to slight œdema, and others to slight thrombosis." Others who favored the vascular theory include Sourdille,[113] Schieck,[114] Aubaret and Sédan,[115] Snell,[116] Kennedy [87] and Bedell.[117]

In 1931 de Saint Martin [118] reported a case of retrobulbar neuritis occurring post partum in which improvement followed intramuscular injections of acetylcholine, and in 1934 Hartmann and Parfonry [119] reported a case of posthemorrhagic amblyopia in which improvement was obtained with acetylcholine after repeated transfusions had been of no avail. (Treatment for the anoxemia with transfusions did not help

112. Cross, R.: Tr. Ophth. Soc. U. Kingdom **33**:43, 1913.

113. Sourdille C.: Clin. ophth. **6**:280, 1900; abstracted, Arch. Ophth. **30**:191, 1901.

114. Schieck, F.: Arch. f. Ophth. **71**:466, 1909.

115. Aubaret, E., and Sédan, L.: Clin. opht. **17**:255, 1928.

116. Snell, A.: New York State J. Med. **33**:370 (March 15) 1933.

117. Bedell, A.: New York State J. Med. **36**:959 (July 1) 1936.

118. de Saint-Martin: Ann. d'ocul. **168**:102 (Feb.) 1931.

119. Hartmann, E., and Parfonry, J.: Bull. Soc. d'opht. de Paris, February 1934, p. 56.

the localized tissue anoxia.) These authors stated that vascular spasm was the cause of the amaurosis.

I [120] recently reported the results of vasodilator therapy in 23 patients who had 27 attacks of acute retrobulbar neuritis. Twenty-nine eyes were involved. There were 9 males and 14 females in the series. No sinuses were opened; no teeth were removed; no vaccines were used, and no foreign protein therapy was employed in any case.

In 18 attacks the average treatment consisted in eight daily intravenous injections of 0.1 Gm. of sodium nitrite. In 4 attacks from three to nine intramuscular injections of acetylcholine bromide (0.1 Gm.) were used. In 1 attack three daily inhalations of amyl nitrite was the only therapy employed. In the other 4 attacks various combinations of the aforementioned drugs were used.

Before treatment, 17 eyes (58.6 per cent) had vision ranging from perception of hand movements to 20/100; after treatment, 25 eyes (86.2 per cent) had vision of from 20/30 to 20/15. In no instance did vision become worse with treatment, but in 4 eyes the final vision was less than 20/200. For the 25 eyes in which vision improved the average duration of loss of sight prior to treatment was 16 days and the average time required for the attainment of the best final vision was 9.7 days. Papilledema and multiple sclerosis were not of unfavorable prognostic significance. The earlier that treatment was instituted, the better were the final visual results. For this reason, I stated that valuable time should not be wasted in searching for foci of infection or other questionable etiologic factors before starting vasodilator therapy.

Of the last 11 attacks in which treatment was given a definite history of exposure to cold or to a sudden change in climatic conditions was obtained in 9. The change was usually from warm to cold weather or from a cold dry to a cold wet atmosphere. Such changes often occur even in the warmer months of the year. For example, May 1938 was a relatively cold month; May 28 was stormy and May 29 was very cold. Four attacks were seen in this particular month, and 3 of them occurred between May 26 and May 30.

In 1 case exposure to cold seemed to be the precipitating factor. The patient, a woman of 23, had walked against a stiff, cold wind on Feb. 22, 1939. The next day, on awakening, she discovered that vision in the left eye was much reduced; that afternoon vision failed in the right eye. On February 24 vision was found to be 4/200 in the right eye and was limited to perception of hand movements in the left eye. She received two intramuscular injections of sodium nitrite and three inhalations of amyl nitrite and then disappeared from the clinic. Information was received from another clinic that on March 7 vision was 20/20 in the right eye and 4/200 in the left eye. After that date she failed to return

120. Duggan, W. F.: Acute Retrobulbar Neuritis as a Manifestation of Acute Localized Tissue Anoxia, Arch. Ophth. **25**:299 (Feb.) 1941.

to the second clinic. (I have recently seen 2 similar cases in which exposure to cold was the only possible etiologic factor. In both cases vision was 20/16 in each eye after vasodilator therapy.)

In this case the reaction was attributed to histamine, formed in the skin and carried to the vessels of the optic nerve by the blood. Horton, Brown and Roth [66] reported an analogous case in which a man collapsed and was unconscious for forty minutes after running about ⅕ mile (320 meters) against a stiff wind at a temperature of 30 F. below zero. The patient did not recover his strength for a week. Had my patient also been unable to walk or had the patient of Horton and associates lost his vision, the diagnosis of neuromyelitis optica could have been made. In other words, the distribution, number and location of lesions determine whether unilateral or bilateral retrobulbar neuritis, myelitis or neuromyelitis optica develops. The differences are those of degree, rather than of kind.

Edwards [121] reported an interesting case of acute retrobulbar neuritis in a woman of 37. Vision in one eye was 4/200, owing to a previous attack of acute retrobulbar neuritis. When her remaining eye was involved, eighteen months later, Edwards used vasodilators, transfusions of blood and inhalations of 100 per cent oxygen. After three weeks her vision had improved to 20/40; a small scotoma was still present. All therapy was directed toward relief of the vascular spasm and tissue anoxia.

Ravin [122] reported 5 cases of optic neuritis in which the drug of choice was erythrityl tetranitrate, a vasodilator, which was given orally. He also gave the patient thiamine hydrochloride, not to relieve a hypothetic vitamin B_1 deficiency but because it acts indirectly as a vasodilator. Visual acuities as determined on several occasions before treatment were 20/70, perception of hand movements, 20/30, 20/70 and 20/200, respectively; after treatment the final visual acuities were 20/30, 20/20, 20/30 +, 20/20 and 20/30, respectively, on several occasions. Ravin's report is of interest because he dedsired to treat the patients orally rather than intravenously. I can corroborate his results, because I have found that the oral administration of erythrityl tetranitrate and nicotinic acid are useful both when used alone and as an adjunct to intravenous injection of sodium nitrite.

Finally, Cordes [123] reported a case of acute retrobulbar neuritis in which vision improved from 2/200 to 20/20 in eight days with vasodilator therapy and a case of optic neuritis in which vision improved from light perception to 20/20 in four weeks with subcutaneous injections of 100 mg. of sodium nitrite.

121. Edwards, D. L.: J. Oklahoma M. A. **34**:201 (May) 1941.
122. Ravin, L. C.: Am. J. Ophth. **26**:188 (Feb.) 1943.
123. Cordes, F. C.: Am. J. Ophth. **26**:916 (Sept.) 1943.

To sum up, acute retrobulbar neuritis is an acute vascular catastrophe occurring in the optic nerve, chiasm or tract, resulting in edema and leading to tissue anoxia and loss of function. Increased capillary permeability, which may be primary, but is probably secondary to arteriolar spasm in most cases, is the basic pathologic process in all cases of this condition. Tissue anoxia occurs because of this capillary change. This pathology is the pathology of allergy, histamine poisoning and shock. The arteriolar-capillary changes are the final common pathway for a number of etiologic agents, which can act on the arterioles or the capillaries or both. Overaction or underaction of certain homeostatic mechanisms explains the condition in many cases. In many cases the disturbance is related to exposure to cold or to a sudden change in the weather. This relationship is causal, rather than casual. On clinical evidence histamine is probably the etiologic agent in these cases. A histamine origin also explains the cases of retrobulbar neuritis attributed to focal infection and to allergy.

UVEA

Iris and Ciliary Body.—Kronfeld,[124] in discussing iritis and iridocyclitis, noted that there are ciliary injection, edema of the iris and exudate in the anterior chamber. The exudate may consist in (*a*) increased protein, (*b*) fibrin, (*c*) cells or (*d*) clumps of cells on the back of the cornea. Nodules may form; when these heal and are absorbed, atrophic areas remain.

According to Davids,[125] nodules which form in the eye may be due to specific or nonspecific factors. He found that nodules (or granulomas) were associated with sympathetic ophthalmia, rheumatic fever and herpetic iritis and pointed out that it is the common tendency to consider such nodules as indicating tuberculosis. Caution in diagnosis is indicated.

In cases of rheumatic uveitis, Marchesani[126] found changes in the uvea, sclera and retina characteristic of so-called rheumatic tissue damage. In the early stages the connective tissue showed fibrinoid swellings; later, nodules of cells developed, composed chiefly of large histiocytes with basophilic protoplasm; finally, the foci changed to connective tissue scars. Giant cells were often present. Unlike the lesions of true tuberculosis, these granulomas produce little tissue reaction, much formation of connective tissue and no caseation. Marchesani expressed the opinion that these changes of "rheumatic" origin represent an allergic-hyperergic inflammation.

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124. Kronfeld, P.: Introduction to Ophthalmology, Springfield, Ill., Charles C Thomas, Publisher, 1938.

125. Davids, H.: Nodule Formation in the Eye, Arch. Ophth. **23**:432 (Feb.) 1940.

126. Marchesani, O.: Rheumatic Uveitis, Arch. Ophth. **23**:431 (Feb.) 1940.

One animal experiment is worthy of report. Spadavecchia [127] sensitized rabbits to horse serum. After a suitable period he injected 10 cc. intraperitoneally, followed by instillation of irritating chemicals into the conjunctival sac. Severe iritis resulted. Control experiments seemed to indicate that the reaction was specific. Among the irritants used were chloroform and histamine. While this was an animal experiment, and therefore not typical of clinical conditions, it may explain those cases of iritic "irritability" which follow trauma to the cornea. In such cases the tears could be the source of the histamine, for Ridley [70] recently reported finding a histamine-like substance in normal tears. Moreover, Ridley's histamine-like substance serves to explain the swollen lids which develop after weeping and which are often seen in cases of acute iritis and iridocyclitis when tearing is copious.

The list of causes of iritis and iridocyclitis includes focal infection, allergy, herpes, syphilis, tuberculosis, endocrine imbalance, rheumatism, gout, antointoxication, acute infectious diseases, brucellosis and the common head cold. Undoubtedly, these conditions have preceded or accompanied anterior uveitis; but is the relationship necessarily one of cause and effect? The ocular changes may be the same as those occurring in the other tissues of the body in these clinically different diseases. All these alleged causes have one thing in common—vascular dysfunction, whether due to histamine, a histamine-like effect associated with allergy or a failure of arteriolar and capillary homeostasis. Moreover, these causes are the alleged causes of every other ocular manifestation of allergy discussed thus far in this essay.

In a recent article I [128] compared acute iritis and iridocyclitis with acute retrobulbar neuritis, acute exudative choroiditis and acute spastic closure of the central retinal artery. In these superficially different lesions the early pathologic changes can be attributed to arteriolar spasm, increased capillary dilatation and permeability and transudation of plasma and white cells into the perivascular tissues. The superficial differences in these various lesions depend on the anatomic character of the affected tissues. Early changes are due to capillary anoxia, which causes tissue anoxia. Acute focal necroses may result; in healing these are replaced by scar tissue or atrophic areas or a combination of the two.

With acute retrobulbar neuritis there are localized edema and round cell infiltration in the optic nerve. Because of the sheath of the nerve, pressure may be exerted on all the fibers in the optic nerve, leading in some instances to total blindness. Yet after healing occurs, only a small bundle of fibers may be permanently affected. This bundle

127. Spadavecchia, V.: Ann. di ottal. e clin. ocul. **66**:241 (April) 1938.

128. Duggan, W. F.: Vascular Basis of Uveal Disease, Arch. Ophth. **24**:1123 (Dec.) 1940.

(as shown by scotometry) consists of the fibers supplied by the spastic arteriole, which is often obliterated.

With acute exudative choroiditis the lesion is subretinal, the edema is pronounced and the retina is secondarily affected. Complete anoxia accounts for the atrophy, while partial or relative anoxia at the edges of the lesion is probably the stimulus for proliferation of retinal pigment there.

With spastic closure of the central retinal artery or one of its branches the spasm is visible, the edema is obvious and the area of edema also corresponds to the area of retina supplied by the involved artery. The loss of function in the field also corresponds to the location and amount of vascular change.

With acute iritis and iridocyclitis there is edema of the iris and the aqueous (prestasis); with peristasis, the cells, which account for the perivascular infiltration in the preceding conditions, pass out into the aqueous because of the loose and spongy nature of the anterior uveal tissue. If the arteriolar spasm is moderate, nodules may form; if severe, focal areas of necrosis occur.

After pointing out that iritis, iridocyclitis, sympathetic ophthalmia and Harada's disease (involvement of the iris, ciliary body, choroid and optic nerve) show only quantitative variations in the extent and severity of the lesions, I reported 11 cases of iritis and iridocyclitis (10 of the acute and 1 of the subacute form) in which only vasodilator therapy was used. (Sodium nitrite was given intravenously and erythrityl tetranitrate by mouth.) The time required for clinical cure was between five and fifteen days; the average time was nine days per case. Minimal amounts of mydriatics were used, and no patient was hospitalized or even told to remain away from work.

Two of the patients with acute iridocyclitis had syphilis; 1 was receiving antisyphilitic treatment; the other was not. These patients were completely cured in five and nine days, respectively.

I also described a case of postoperative iridocyclitis which followed an uncomplicated cataract operation. The condition could have been diagnosed either as early sympathetic ophthalmia or as endophthalmitis phacoanaphylactica. Injections of milk, use of salicylates and frequent instillations of atropine were without effect. Four weeks after operation the patient received four intravenous injections of sodium nitrite and oral doses of erythrityl tetranitrate (15 mg.) twice daily by mouth. After ten days the eye was white and the tension, which had been low, was normal.

In my conclusions, I stated that the striking and rapid improvement which followed vasodilator therapy in these cases was of fundamental biologic importance. I suggested histamine as a "likely etiologic agent because (1) histamine constricts arterioles and both dilates and increases

the permeability of capillaries; (2) histamine can account for cases ascribed to allergy, focal infection and cold, and (3) histamine is set free when tissue is traumatized."

Arkhangelskiy [129] stated nine years ago that postoperative cyclitis was due to mechanical irritation of the ciliary nerves and that a neurohumoral factor must be considered in any theory concerned with the causation and development of this lesion. He did not mention antidromic impulses or axon reflexes or imply that histamine might be the neurohumoral agent, but he expressed the opinion that dental infection was also a factor of importance.

Kennedy, Wortis and Wortis,[89] after mentioning that it is commonly known that vascular accidents occur in the brain in the course of an untreated syphilitic infection, stated:

> The very fact that many of these episodes are rapid to occur and clear up without treatment is evidence in favor of the possibility of angiospasm being the causative mechanism.

What is true for the brain should be true for the eye. In cases of untreated infections the iritis may be of reflex origin; in cases in which treatment is employed it may be an anaphylactoid reaction. In either case its origin is vascular.

During the past two years I have treated 6 additional patients with acute iritis and iridocyclitis with vasodilators alone. In 1 of these patients the condition followed a cataract operation. All patients were clinically cured in from four to seven days. No teeth were extracted; no salicylates were given; no foreign protein therapy was instituted, and minimal amounts of atropine or scopolamine were used. The results were uniformly good, and the patients were spared the loss of time from work, the expense of hospitalization and the discomfort and malaise which often accompany "shock" therapy.

In conclusion, it may be stated that acute iritis and iridocyclitis are manifestations of vascular dysfunction. The clinicopathologic changes represent varying degrees of prestasis, or liquor stasis, and peristasis, or leukostasis, which are due to increased capillary permeability. These capillary changes may be primary, or, what is more likely, because of the favorable response of these conditions to vasodilator therapy, they are secondary to arteriolar spasm. The pathology is that of allergy, of histamine poisoning and of epinephrine poisoning. Not all cases have the same cause, but in all cases the origin is vascular. Vasodilators act by ensuring an adequate supply of oxygen-containing blood to the capillaries and tissues, thereby relieving capillary and tissue anoxia.

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129. Arkhangelskiy, V. N.: Sovet. vestnik oftal. **8**:10, 1936; abstracted, Arch. Ophth. **16**:712 (Oct.) 1936.

In all cases the condition may be considered as of allergic origin, but such a conception must be broadened to include forms due to physical allergy, to histamine and to overaction of the sympathetic nervous system. The focal nature of the lesions must be due to hypersensitivity of one or more arteriolar-capillary units in the anterior part of the uvea. This hypersensitivity of terminal units explains only why iritis develops in some cases, iridocyclitis in others and choroiditis in still others. There is a definite age incidence for these lesions, which may be due in part to endocrine influences, relative avitaminosis or imbalance of the autonomic nervous system. The vascular changes are the final common pathway for a number of etiologic factors. In most cases there are probably multiple causes, no one of which by itself could produce acute iritis or iridocyclitis but which, acting together, shift the reactions in the tissues from the zone of normal physiology into the zone of pathology.

Acute Exudative Choroiditis.—Many years ago, Moore [84] asserted that acute choroiditis was similar in many respects to embolism of the central retinal artery or one of its branches. He stated that such a hypothesis was more plausible than attributing the lesions to tuberculosis. In 1925 closure of the retinal artery was attributed to emboli in most cases. With increasing knowledge of vascular physiology, the tendency is usually to attribute the condition to spasm. It is not unlikely that today Moore would alter his statement and attribute acute exudative choroiditis to spasm of the choroidal arteries rather than to embolism.

In 1939 Heath [130] mentioned the lack of evidence supporting tuberculosis as a cause of acute choroiditis, the absence of even questionable foci of infection in many cases and the presence of spasm of retinal arteries in 4 of his 24 cases. Among the conditions credited with causing acute choroiditis are chilling, pregnancy, lactation, influenza, intestinal infection, head colds, focal infection, multiple sclerosis and allergy. The etiologic factors are strikingly similar to the causes of acute retrobulbar neuritis, acute iritis and even closure of the central retinal artery. Heath also stated that "the frequent and severe involvement of the vessels has led many to suppose that the condition is primarily vascular." He personally did not favor this theory.

Recently I [131] reported 5 cases of acute exudative choroiditis (3 cases were of the juxtapapillary type) in which I used only vasodilator therapy. I gave twelve to fourteen intravenous injections of sodium nitrite and erythrityl tetranitrate by mouth. One patient, who was not materially improved, also had closure of the inferior division of the central retinal artery. Before treatment the other 4 patients had vision

130. Heath, C.: Brit. J. Ophth. **23**:289 (May) 1939.

131. Duggan, W. F.: Acute Exudative Choroiditis, Arch. Ophth. **23**:930 (May) 1940.

of 20/30—, 8/200, 20/100 and 20/100, respectively. After treatment the final visual acuity and the time required for cure were 20/20— (nine days), 20/40— (twenty-one days), 20/20— (nineteen days) and 20/30— (nine days), respectively. The patient attaining vision of 20/40— was not seen again for six weeks, at which time vision was 20/20. The patient who attained visual acuity of 20/30— had had vision of 20/30 for a year preceding the attack because of two previous attacks. In these 4 patients the lesions in the fundus subsided completely in fourteen, twenty-one, nineteen and twenty-nine days, respectively.

Cordes [123] reported equally good results in 2 patients who were treated similarly.

I commented on the basic similarity of this lesion, acute retrobulbar neuritis and acute spastic closure of the central retinal artery. All three conditions are manifestations of tissue anoxia resulting from arteriolar spasm and increased capillary permeability. I suggested histamine as a possible etiologic factor because this could explain the cases occurring in cold weather as well as those attributed to focal infection. I also noted that the pathologic changes of histamine poisoning and those resulting from overdoses of epinephrine were similar and that both substances produced lesions by causing varying degrees of prestasis, peristasis and stasis.

The pathology of acute choroiditis is the pathology of allergy, and both are manifestations of a disturbance of vascular physiology. For this reason I said: ". . . the use of vasodilators for the treatment of this condition has a sound physiologic and pathologic basis."

Choroidosis Serosa Centralis.—There is a condition called serous retinopathy by Duke-Elder [132] which has been variously attributed to allergy, focal infection and "toxemia." Some authors believe it to arise from retinal angiospasm. Among the diagnoses offered by this group are retinitis centralis (Asayma), central angiospastic retinitis (Horniker), central angiospastic retinopathy (Gifford and Marquardt), retinal capillarosis (Cattaneo), angioneurotic macular degeneration (Candian) and juvenile exudative macular retinitis (Junius). Cattaneo [133] stated that the lesions may be macular, paramacular or disseminated, and he expressed the belief that circinate retinitis, senile macular exudative retinitis and disciform degeneration of the macula are also due to retinal angiopathy.

Another group of observers (Masada, Batten, Oguchi, Abe and Riehm) have described similar lesions but attributed them to subretinal

132. Duke-Elder, W. S.: Textbook of Ophthalmology, St. Louis, C. V. Mosby Company, 1941, vol. 3, pp. 2592-2594.

133. Cattaneo, D.: Ann. di ottal. e clin. ocul. **65**:721 (Oct.) 1937.

edema originating from the choriocapillaris. Walsh and Sloan[134] reviewed this aspect of the subject fully in 1936. They pointed out that moderate diminution of central vision, a positive scotoma, micropsia and, usually, transitory hyperopia were the important signs and symptoms. In general, the scotoma was larger for blue than for red, indicating a lesion interfering with the function of the rods and cones. They offered the term "idiopathic flat detachment of the macula" to describe the condition, and they suggested that focal infection or a circulatory disturbance, either angioneurotic or allergic in origin, must be considered as an etiologic factor.

The advisability of including cases of disciform degeneration of the macula in this group is based on Cattaneo's opinion and on a recent article by Verhoeff and Grossman,[135] who described 3 cases and reviewed the literature. For 1 of their cases they stated: ". . . the possibility cannot be excluded that the blood was derived from the choriocapillaris by diapedesis"; and for another case they said: ". . . there was a serous exudate occurring primarily beneath the pigment epithelium . . . and elevating the retina here in the form of a mound." Later, they said ". . . the observations in our cases do not exclude the possibility of a localized vascular lesion." Verhoeff and Grossman[136] closed the discussion of their article with the following words:

> . . . a typical lesion is due to organization of a hemorrhagic extravasation which is primarily beneath the pigment epithelium. In some cases the hemorrhage may be due to urticaria. I can even bring my favorite factor, allergy, into the question.

It is difficult to differentiate lesions due to choroidal angiopathy from those due to retinal angiopathy. They have the same etiologic background. However, this differentiation can be made by scotometry. In the cases of choroidal origin there is always a scotoma which is as large for a blue test object as for a red test object of the same size, or even larger. Micropsia and transitory hyperopia occur in the cases with but slight depression of the visual acuity, and elevation of the macular region (up to 3 or 4 D. in some cases) is always present. The retinal alterations (white spots, pigmentation or depigmentation) are the most obvious, but the least important, changes in the fundus.

In my opinion, these subretinal lesions bear the same relation to acute exudative choroiditis as an urticarial wheal bears to erythema nodosum. These lesions represent prestasis, or liquor stasis, while acute exudative choroiditis and erythema nodosum represent varying

134. Walsh, F. B., and Sloan, L. L.: Am. J. Ophth. **19**:195 (March) 1936.

135. Verhoeff, F. H., and Grossman, H. P.: Pathogenesis of Disciform Degeneration of the Macula, Arch. Ophth. **18**:561 (Oct.) 1937.

136. Verhoeff, F. H., and Grossman, H. P.: Pathogenesis of Disciform Degeneration of the Macula, Arch. Ophth. **19**:467 (March) 1938.

degrees of peristasis and stasis; the vascular catastrophe is so severe that focal necroses occur in the latter conditions.

I [137] reported 13 cases of central subretinal edema. I prefer the term "choroidosis serosa centralis" to designate this condition due to choroidal angiopathy. In all cases it was considered to be a manifestation of localized capillary and tissue anoxia and may be interpreted as due to allergy because the lesion is fundamentally a wheal. Vasodilators were used to increase the supply of oxygen-containing blood to the tissues involved. An analysis of these cases is of interest.

In the cases (7) of less severe central subretinal edema there was only a central scotoma for blue and, in some instances, a scotoma for a 1 mm. white test object at 1,000 mm. Visual acuity varied from 20/50 to 20/30 before treatment; after treatment, it varied from 20/30 to 20/15. The macular region was elevated from 1 to 2 D. before treatment. The swelling subsided with improvement in vision. Complete cure required from five to twenty-one days (average, ten days).

Three other cases were typical instances of early disciform degeneration of the macula. In the first, a woman of 48 had vision of 20/100; with intravenous injections of sodium nitrite vision improved to 20/30 in sixteen days. In the second, a man of 61 had vision of 20/30—; with treatment it improved to 20/20— in one week. This was maintained for one month, after which the vision suddenly decreased to 12/200, owing to a large subretinal hemorrhage. In the third case a woman of 65 had vision of 20/100; this improved with vasodilator therapy to 20/50 in thirteen days and was maintained for three months. After this the patient failed to return for further observation. One other patient, a man of 56, whose vision had been poor for four or five years, had a condition suggestive of disciform degeneration of the macula. Vision was 20/200 in each eye; the macular regions were elevated from 2 to 3 D., and there was a central scotoma for white and blue; the scotoma for red was smaller than the scotoma for blue. After twenty-three intravenous injections of sodium nitrite (0.1 Gm.), in ten weeks vision improved to 20/50— and 20/70—, the scotomas decreased in size and density, and the macular elevation had decreased to about 1 D.

Many of the 13 patients gave a history of other allergic lesions. One patient had had two attacks of acute retrobulbar neuritis; both attacks cleared in a few days with the same vasodilator therapy. Another patient had had bilateral retrobulbar neuritis thirty years earlier, with permanent field defects and some atrophy of the optic nerve. As his fields had been plotted prior to the attack of choroiditis serosa centralis, it was easy to diagnose the presence of the new submacular

137. Duggan, W. F.: Choroidosis Centralis Serosa, Arch. Ophth. **27**:123 (Jan.) 1942.

lesion. (I have recently seen another patient who had both lesions.) One patient had lost useful vision in her other eye twelve years before the present attack, after acute exudative choroiditis at the macula. Another patient suffered from attacks of urticaria. In 1 patient the subretinal lesion developed fourteen hours after an intravenous injection of sodium iodide and sodium salicylate. Finally, a girl of 20 had onset of both central subretinal edema and Bell's palsy on the same side after walking 1 mile (1.6 kilometers) to work on Jan. 22, 1940, when the outdoor temperature was 28 F. With intravenous injections of sodium nitrite, the ocular lesion cleared in eight days and Bell's palsy in eleven days. The disturbance in this case could well have been due to hypersensitiveness to cold and therefore could be attributed to histamine, formed in the skin and then carried by the blood to the arterioles and capillaries in the choroid and in the facial nerve.

Cordes [123] reported a similar case of a woman aged 34. Her vision improved from 20/200 to 20/20 in one week with daily subcutaneous injections of sodium nitrite and three daily small doses of typhoid vaccine given intravenously.

Horniker,[138] who used the term central angiospastic retinitis, expressed the belief that exposure to cold was a causative factor in some of these cases and that vasodilators were of value.

Gifford and Marquardt [139] stated preference for the term "central angiospastic retinopathy." They used antispasmodic treatment with benefit in their 8 cases. They also expressed the belief that exposure to cold should be avoided by patients with this lesion.

In a later article, Gifford [140] reported on 23 additional cases of central angiospastic retinopathy (choroidosis centralis serosa?). He stated that peripheral angiospasm is the cause of these macular lesions and that protection against cold and abstinence from tobacco are indicated for patients with such a condition. His treatment included administration of papaverine intravenously; typhoid vaccine intravenously; phenobarbital, a preparation of theobromine and phenobarbital (Theominal) or a deproteinated pancreatic extract (Depropanex) intramuscularly; nicotinic acid or the vitamin B complex; sodium nitrite by vein; neostigmine by mouth; thyroid extract in cases of lowered basal metabolism, and a regimen including plenty of rest and avoidance of fatigue and nervous strain when it seemed practical. No patient

138. Horniker, E.: Ann. di ottal. e clin. ocul. **55**:55, 1927; Arch. f. Ophth. **123**:286, 1929; Klin. Monatsbl. f. Augenh. **98**:487, 1937.

139. Gifford, S. R., and Marquardt, G.: Central Angiospastic Retinopathy, Arch. Ophth. **21**:211 (Feb.) 1939.

140. Gifford, S. R.: Evaluation of Ocular Angiospasm, Arch. Ophth. **31**:453 (June) 1944.

received all the aforementioned antispasmodics, but most of them received various combinations of them.

Cordes [141] has also reported on a type of foveomacular retinitis observed in the United States Navy. Approximately 176 cases were studied in detail, but many more cases were seen. Clinically, this retinitis resembled Duke-Elder's central serous retinopathy or Gifford's central angiospastic retinopathy. Vasomotor instability, emotional upsets, fear, worry, anger and the excessive use of tobacco, all of which, either alone or in various combinations, can, and often do, produce angiospasm, were mentioned by Cordes in his discussion of the etiology of this lesion. He concluded that the etiologic factors deserved further study, with special consideration to peripheral vascular disease and angiospasm, and that the use of vasodilators in the early stages seemed beneficial.

Finally, Bothman,[142] after abstracting a case of central edema with blurring which was reported by Brinckerhoff and in which normal vision was regained after treatment with vasodilators and typhoid vaccine, said, "We believe that this type of lesion is due to allergy."

I believe that choroidosis serosa centralis is often a manifestation of allergy and that disciform degeneration, which occurs in the older patients, differs only in degree from this condition in young people. Both are manifestations of tissue anoxia. Vascular dysfunction causes the tissue anoxia, and allergy is often the cause of the vascular dysfunction. The use of vasodilators in this condition is based on the pathologic physiology of the lesion.

SCLERA

The nonpyogenic scleral "inflammations," which Duke-Elder [143] divided into episcleritis (nodular episcleritis and episcleritis periodica fugax) and scleritis (anterior, brawny and posterior scleritis, and sclerokeratitis) have been ascribed to gout, rheumatism, tuberculosis, syphilis, allergy, focal infection and menstruation. Regarding these conditions, Friedenwald [144] stated:

> . . . The etiology . . . seems to be related to that of the non-specific inflammations of the iris, ciliary body and choroid. . . . The histological picture presented by all of these cases consists of a necrosis of some of the scleral fibers with surrounding edema and round cell infiltration.

If the words "scleral fibers" are replaced by "nerve fibers," the description would apply to acute retrobulbar neuritis, multiple sclerosis or neuromyelitis optica.

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141. Cordes, F. C.: Am. J. Ophth. **27**:803 (Aug.) 1944.

142. Bothman, L.: The 1944 Year Book of the Eye, Ear, Nose and Throat, Chicago, The Year Book Publishers, Inc., 1944, p. 149.

143. Duke-Elder,[132] 1938, vol. 2, pp. 2044-2069.

144. Friedenwald, J. S.: The Pathology of the Eye, New York, The Macmillan Company, 1929, pp. 67-69.

Duke-Elder's description is more complete. He stated:[143]

> The lesion is characterized especially by the presence of mononuclear lymphocytes, tightly packed masses of which make up the bulk of the inflammatory nodules or the areas of diffuse swelling. . . . In the superficial episcleral lesions the conjunctiva is infiltrated in its sub-epithelial layer, as well as the superficial parts of the sclera, the laminae of which are separated by œdema and surrounded by rows or spindle-shaped masses of lymphocytes. In these lesions extreme vascular engorgement and lymphatic dilatation occur almost invariably (Schirmer, 1895; Uhthoff, 1900). In the deeper lesions the same infiltration occurs.
>
> In the milder cases the inflammatory exudation may disappear leaving little or no trace; but in most cases of any degree of severity necrosis of the cells and fibres results while the new vessels undergo an obliterating endarteritis, or alternately fatty or hyaline degeneration may ensue. The necrotic tissue is then slowly absorbed; and as a rule proliferation of new fibrous tissue replaces the atrophy, leaving . . . a scar.

It must be apparent that the foregoing description is a description of allergy. The edema is due to increased capillary permeability, and the focal necroses are due to arteriolar spasm, which may also be the cause of the increased capillary permeability. This is borne out by the fact that in cases of severe scleritis there is obliteration of the arterioles, just as in case of healed acute choroiditis one or two narrowed or obliterated choroidal vessels can be seen in the floor of the lesion. However, this arteriolar lesion is primary rather than secondary, as is commonly believed.

Purtscher[145] recently reported the case of a man of 67 who had serous tenonitis of the left eye and extensive choroidal detachment. A few days later the right eye was similarly affected. Still later retinal detachment and hypotony developed. After six months the detachments and hypotony disappeared. Purtscher asserted that the serous tenonitis and choroidal detachment represented an edema which was secondary to posterior scleritis; the posterior scleritis was ascribed to a vasomotor neurosis on an allergic basis.

On the assumption that many of these scleral inflammations are manifestations of localized tissue anoxia due to varying degrees of arteriolar spasm and increased capillary permeability, whether the results of allergy, histamine or overaction of the sympathetic nervous system, treatment with vasodilators only was instituted in 5 cases (intravenous injections of 100 mg. of sodium nitrite and administration of erythrityl tetranitrate by mouth). These cases, which have been reported in full elsewhere,[146] are summarized as follows:

> Case 1.—W. P., a man of 58, was seen on March 24, 1938, with episcleritis of the right eye. Symptoms had been present for six days. He received 30 mg. of erythrityl tetranitrate twice daily for five days and sodium nitrite intra-

145. Purtscher, E.: Klin. Monatsbl. f. Augenh. **94**:12 (Jan.); 141 (Feb.) 1938.

146. Duggan, W. F.: Role of Anoxia in the Production of Episcleritis and Scleritis, Arch. Ophth. **25**:113 (Jan.) 1941.

venously on March 24 and 29. The nodule disappeared in two days, as did the symptoms. On the seventh day (March 31) only two dilated venules indicated the site of the former lesion. There was no immediate recurrence.

CASE 2.—W. W., a man of 30, was seen on Aug. 13, 1938, with episcleritis of the right eye. Symptoms had been present for one month. He had had similar attacks in both eyes in the past. He received five daily injections of sodium nitrite and then took 15 mg. of erythrityl tetranitrate twice daily until August 21. On August 17 the right eye was free from symptoms and practically white. No recurrence took place during the next three weeks.

CASE 3.—M. M., a man of 61, was seen on Sept. 30, 1938, with scleritis of the right eye, present for about nine days. Pain was an outstanding symptom. He received six daily injections of sodium nitrite, followed by administration of erythrityl tetranitrate by mouth for several days. Pain was relieved after the first injection; the tenderness disappeared after the fourth injection, and on October 7 the eye was almost completely white. He failed to return to the clinic for further observation.

CASE 4.—Mrs. C. H., aged 68, was seen on Jan. 14, 1940 with moderately severe brawny scleritis of both eyes, which had been present in the right eye for two days and in the left eye for one day. The only ascertainable cause was exposure to cold weather, on January 11 and 12. She was immediately given an injection of sodium nitrite and 15 mg. of erythrityl tetranitrate by mouth in the evening. When she returned, at my request, on January 18, she was free from symptoms. There was only a tiny patch of episcleral congestion nasal to the limbus in each eye. A second injection of sodium nitrite was given. On January 22 both eyes were completely white.

CASE 5.—I. S., a man of 65, was seen on Jan. 21, 1940 with episcleritis of the left eye, which had been present for about one week. The chemosis of the conjunctiva over the nodule was so intense that the conjunctiva protruded between the closed lids. His history was without significance except for exposure to cold on January 15. He received injections of sodium nitrite on January 21 and 22 and took 30 mg. of erythrityl tetranitrate for three nights. The chemosis had disappeared on January 22. On January 24 the eye appeared entirely white and normal. There have been no recurrences to date.

Vision was not affected in any of these cases. No therapy other than that mentioned was used in any case. Even mydriatics were not used except in examination of the fundi at the first visit of each patient. The time required for a clinical cure varied from three to eight days. This treatment is not empiric but is based on a consideration of the pathologic physiology in these cases. In all cases the inflammation could have been ascribed to allergy. In cases 4 and 5, in my opinion, however, the condition was due to exposure to cold and could be ascribed to histamine.

MISCELLANEOUS CONDITIONS

No mention has been made of the noninfectious inflammations of the lids and conjunctiva which occur after contact with drugs and cosmetics. While these are probably forms of drug allergy, the relation of cause and effect is obvious, and a cure usually follows removal of the irritant.

Vernal conjunctivitis and trachoma are considered by many ophthalmologists to be manifestations of allergy. Inasmuch as I have had no opportunity to treat these conditions with vasodilators in order to discover whether or not they represent unusual types of localized tissue anoxia, I prefer not to burden the reader with a recapitulation of the literature.

For many years it has been known that cataract is occasionally associated with eczema, neurodermatitis and other lesions of the skin attributed to allergy. Daniel [147] discussed this in 1935. Since then, except for reports of cases, little of importance has appeared in the literature. Moreover, these cataracts must be treated surgically in the manner prescribed for other cataracts.

In many cases the onset of acute dacryocystitis may be due to allergic changes in the walls of the sac, similar to that occurring with vasomotor rhinitis (or noninfectious coryza, as it was called by a correspondent in the *British Medical Journal*). Secondary invasion of the edematous, ischemic walls of the sac by pyogenic organisms (Findlay [18]) usually necessitates surgical intervention.

Acute dacryoadenitis may also be allergic in the sense that there is intense edema of the gland, due to increased capillary permeability. Here, release of tension by opening the gland usually results in cure, just as a decompressing operation relieves acute glaucoma.

Migraine may be accompanied with spasm of the retinal artery, paralysis of ocular muscles and scotomas. It is considered to be due to spasm of cerebral arterioles, followed by development of a "wet" brain, due presumably to increased capillary permeability. The most effective types of therapy are those which (1) paralyze the sympathetic vasoconstrictors, (2) actively dilate arterioles or (3) supply pure oxygen (Alvarez). Whether migraine is due to allergy, endocrine influences or overaction of the sympathetic nervous system is still *sub judice*. In many cases migraine is probably of allergic origin. Vasodilator therapy seems to be of value.

NATURE OF VASCULAR SPASM

While there are many articles dealing with the role of vascular spasm in particular diseases or in single cases, the best presentation of the subject as a whole from the viewpoint of the experimental pathologist is Nedzel's [148] monograph.

According to Nedzel, the activities of the autonomic nervous system, the endocrine glands and the chemical and metabolic processes of the body are intimately related. The demand of the cells for nutrition depends on environmental conditions and is controlled by the

147. Daniel, R. K.: Allergy and Cataracts, J. A. M. A. **105**:481 (Aug. 17) 1935.

148. Nedzel, A. J.: Vascular Spasm: Experimental Studies, Illinois Medical and Dental Monographs, Urbana, University of Illinois Press, 1943, vol. 3, nos. 3-4.

proper functioning of these three systems, whose changing behavior is reflected by the vascular system, particularly the peripheral circulation, since the capillaries are the medium through which oxygen and foodstuffs reach the cells and waste products are carried away.

Therefore, it is reasonable to concentrate on the vascular system as the final regulator of the functions of the cell in its readjustments to the changing demands on its activities. The function of the vascular bed is to protect the organism from injurious exogenous and endogenous agents and to sustain normal life. Any inadequacies in the behavior of the terminal blood vessels will lead to impaired function, with resulting injury of particular groups of cells and the consequent production of disease.

In Nedzel's words:

> The transient variations in the resistance of the small blood vessels . . . depend on the changes in tone of their walls. Hypertone . . . and hypotone . . . each [of] . . . which may occur simultaneously in the whole body or in a large part of the body, interferes little with the passage of blood to the tissue, and hence does not impair the process of nutrition.
>
> Another type of reaction is "vascular spasm." It is an exaggerated state of hypertone, and, what is more important, it is limited to a certain region, organ, or part of the body, or even to one artery. Spasm, in this sense, is always a localized phenomenon, a pathological occurrence, a diversion from the average amplitude and size of the normal ARS phase[149] of Petersen . . . the local phenomenon of vascular spasm means practically a complete stop, or a greatly diminished blood supply to the particular region, during a definite time interval, shorter or longer, but always exceeding the normal demand imposed by the environment. . . .
>
> . . . vascular spasm . . . is purely a functional phenomenon which is manifested by different pathological symptoms. Yet . . . [spasm] if greatly pronounced or prolonged, or both, may precipitate disease in the organ or bodily region in which the disturbance is centered. This view has both clinical and experimental evidence to support it. . . .
>
> As the metabolism of the cell is dependent on oxygen, any appreciable diminution in available oxygen precludes normal cell function. For this reason, anoxic phenomena become increasingly important in studies of pathologic conditions of the human body, as well as in therapy. . . .
>
> The functional activity of the vascular bed appears to be of much significance in the development of many diseases, the etiology of which is attributed to other causes. Many different diseases themselves and different symptom-complexes can be explained on a vascular basis.
>
> . . . Basic disturbances—spasms in vascular beds—appeared [in animal experiments] in different regions and organs in varying degrees, thus leading to the formation of lesions in widely separated organs. These lesions are bases for different diseases, and yet their etiology is the same . . .
>
> . . . any factor which leads to vascular episodes in the body may cause one or another of several diseases, diseases which are very different clinically in their localization and manifestation.

149. ARS phase is a term used to denote the predominance of anabolism, reduction and vascular constriction (spasm).

While Nedzel did not discuss allergy as an entity, he did mention that some investigators have evoked allergy as the cause of acute rheumatic fever and of multiple sclerosis. He then went on to show that, according to his experiments and according to the work of other investigators, both these diseases are of vascular origin and that transitory periods of localized anoxia can account for the pathologic changes observed in these diseases. Throughout his presentation he repeatedly stated that sudden changes in the meteorologic environment constitute a common cause of anoxia due to vascular spasm and that persons with an unduly labile vascular system are the most susceptible. Undoubtedly, he would agree that these patients are allergic to their environment, that this is a variety of physical allergy, and that the basic lesion is arteriolar spasm and increased capillary permeability.

ALLERGY AND THE WEATHER

Petersen,[150] a pathologist, has written extensively and logically about the relation of allergic manifestations to the weather. He used urticaria as an example and proved (in my opinion) that it is not necessary to assume that urticaria is always due to a specific antigen-antibody reaction. A few quotations may be of interest.

In discussing menstrual urticaria, he stated:

> Today we have taken over the same reasoning [that the bacterium is the whole story in etiology] and are searching deeply and frequently successfully for offending protein and other sensitizing agents. Again we disregard the constitutional—the conditioning factor of the individual patient. . . . Personally, I doubt much the possibility of ever desensitizing in the true immunological sense. . . .
>
> Either we assume that we deal . . . with an antigen that is constantly present, but with varying susceptibility and resistance on the part of the patient, or we must conclude that transient vasomotor alterations in the skin, incidental to and characteristic of this unstable type of individual, produce the lesions.

In a further chapter on the urticarias, he stated:

> Today, with the vogue of specific sensitization, we think only in terms of allergins, of antibody mechanisms [page 387].
>
> We deal with more diseases of this type [urticaria] in America than in Europe merely because the environmental conditions are more severe and the opportunity for vascular instability becomes greater [page 388].

If one may assume that any aseptic lesion produced by increased capillary permeability, with or without a preceding arteriolar spasm, is basically an allergic lesion, then, as I have shown, acute glaucoma, iritis and iridocyclitis are manifestations of allergy in some cases, though not necessarily of allergy due to an antigen-antibody reaction. Petersen summarized 40 such cases and furnished the necessary meteorologic data. Every attack of acute glaucoma, iritis or iridocyclitis could be related to

150. Petersen, W. F.: The Patient and the Weather, Ann Arbor, Mich., Edwards Brothers, Inc., 1934, vol. 2, pp. 350-487.

a sudden alteration in the meteorologic environment, and the majority of them were referable to a polar infall (rising barometric pressure and falling temperature). It is the polar infall or passage of a cold front which is the cause of the "ARS" (anabolism, reduction, vascular spasm) phase in the body, and when this phase is present there is tissue anoxia of one or another organ or tissue or portion of a tissue. This localized anoxia, due to arteriolar spasm and increased capillary permeability, gives the localized picture of allergy. It may well be that in the cases which can be related to weather changes one is dealing with an actual hypersensitivity or allergy to weather. Certainly, the condition in these cases must be a variety of physical allergy.

Petersen [151] also reported on the environmental changes (temperature, barometric pressure and rainfall) which occurred in some of the cases in which I employed vasodilator therapy, and which are referred to earlier in this article. In the series of 13 cases which he studied, and which included instances of acute iritis, iridocyclitis, episcleritis, scleritis, choroiditis and retrobulbar neuritis, the onset in every case and the exacerbations in several cases were related in point of time to the passage of a polar air mass. Petersen's comment was:

> . . . any extreme in the environmental situation, whether toward cold or toward undue heat, is apt to find reflection in clinical symptoms for the simple reason that such changes entail major vasomotor adjustment. While any one of many environmental factors . . . may act as a precipitating force, the weather episode, on the background of season, is the most common of the energy inpacts that are effective, for the biologic effect is apt to be prolonged. The vascular spasm may exist for hours or even days, is subject to summation with repetition of environmental change and is, in addition, universal in its effectiveness in the population at large. . . . The meteorologic episode is universally effective, and the clinical reflection will be found in any organ or tissue.

Mills [152] stated:

> Short cycle weather changes bring startling alterations in health and physiologic functions, alterations with which physicians should be thoroughly aware.

I believe that man's reactions to the ever changing sea of air in which he lives constitute, in an unstable person, one of the major causes of disease and that allergy or, better, hypersensitivity or, still better, vasoneuropathy of physical origin (Urbach) is a pathologic reaction to a sudden change in this sea of air.

COMMENT

Only eight years ago Pickworth,[153] in discussing the physiology and pathology of mental and emotional states, said:

151. Petersen, W. F.: Weather and Ocular Pathophysiology, Arch. Ophth. **29**:747 (May) 1943.

152. Mills, C.: Medical Climatology, Springfield, Ill., Charles C Thomas, Publisher, 1939.

153. Pickworth, F. A.: Brit. M. J. **1**:265 (Feb. 5) 1938.

Superstition demands an infinitely more complex control of the already complex nervous system, and thus hinders study of a humbler control by the vascular system.

The clinical significance of regional vascular irregularities, however, needs many more years of further patient study.

And Petersen,[154] in 1934, said:

We are accustomed to regard the blood supply to the tissues as uniformly adequate unless gross pathological disturbances exist . . . we seldom consider the possibility of regional or organ inadequacy of vascular function unless the clinical manifestations are obvious.

As a matter of fact, variation in the oxygen supply to the tissues is probably one of the most common of events and dysfunction or inadequacy of the mechanism that has to do with oxygen supply is probably the fundamental cause of all disease.

Poncher,[155] in a discussion of purpura, stated that the factors concerned with increased capillary permeability are hereditary, environmental, allergic, vasomotor, endocrine and dietary influences and, finally, lack of oxygen.

In my opinion, allergy of the ocular tissues may be considered an acute localized vascular catastrophe which is the result of arteriolar spasm or increased capillary permeability or both. Tissue anoxia and loss of function are the immediate results.

Capillary permeability is increased beyond physiologic limits by lack of available oxygen, by excessive arteriolar constriction and by histamine.

Lack of available oxygen is often due to an anemic or histotoxic anoxemia, in which the blood is unable to carry adequate amounts of oxygen. However, a physiologic anoxemia may occur in which, owing to an alkalosis (which may be due to primary carbon dioxide deficit, as in overbreathing, or to excessive intake of alkali), the dissociation curve of oxyhemoglobin is shifted to the left, so that the oxyhemoglobin does not dissociate normally in the capillaries but retains its attached oxygen. A lowering of the temperature of whole blood also shifts the dissociation curve of oxyhemoglobin to the left.

Arteriolar spasm may be caused by overaction of the sympathetic nervous system; by an excess of epinephrine in the circulating blood; by nicotine; by histamine or histamine-like substances, and by a decreased formation or an increased destruction of acetylcholine, the vasodilator hormone of the body.

Even the vitamins may act via the capillaries and arterioles. Lack of ascorbic acid increases capillary permeability. Thiamine according to Minz,[156] acts by augmenting the action of acetylcholine; Spies, Bean

154. Petersen,[150] p. 11.

155. Poncher, H. G.: Purpura as a Symptom in Pediatric Practice, J. A. M. A. **104**:1690 (May 11) 1935.

156. Minz, B.: Presse méd. **76**:1406 (Sept. 21) 1938.

and Stone [157] and many others have reported that nicotinic acid dilates arterioles, and it is known that riboflavin is concerned with oxidative processes.

Excess or deficiency of endocrine secretions may also alter reactions of blood vessels. Urticaria and episcleritis have been attributed to menstruation. Reynolds [158] reported that estrogen substances are cholinergic in that they apparently increased the acetylcholine content of the rabbit uterus. (Many persons with hypothyroidism are abnormally sensitive to cold.) Therefore, lesions attributed to endocrine imbalance may be due to angiospasm resulting from temporary failure of the hormonal mechanism concerned with maintaining homeostasis.

Histamine or histamine-like bodies are of major importance in any study of allergy for the following reasons:

1. The histamine theory of anaphylaxis, first formulated by physiologists, has never been disproved.

2. Histamine can account for all lesions attributed to allergy and focal infection.

3. Histamine is formed in the skin after exposure to cold. This accounts for the high incidence of allergic lesions in the winter and early spring, as well as for those which occur after a sojourn in air-cooled theaters or restaurants.

4. Histamine is formed in heated tissues. This explains the manifestations of allergy following treatment with heat produced artificially.

5. Histamine is formed in the gastrointestinal tract. Failure of the normal detoxifying mechanism provides a ready supply of histamine.

6. Histamine is released by antidromic nerve impulses.

7. Histamine is formed in traumatized tissue.

8. Histamine is found in leukocytes (Code,[159] Dale). Because of this fact, the perivascular round cell infiltration may both perpetuate the original lesion and stimulate the formation of new lesions. Such a hypothesis is particularly applicable to sympathetic ophthalmia, as I have indicated elsewhere.

9. Histamine intensifies positive reactions to cutaneous and intradermal tuberculin tests. Therefore, a positive reaction to the Mantoux test is not proof that an allergic ocular lesion is due to tuberculosis.

10. Histamine causes both arteriolar spasm and increased capillary permeability, so that plasma, white cells and, at times, red blood cells pass out into the tissues. This is the pathologic basis of allergy.

The pathologic changes of allergy are due to vascular reactions which are physiologic in nature but pathologic in degree. These vascular

157. Spies, T. D.; Bean, W. B., and Stone, R. E.: The Treatment of Subclinical and Classic Pellegra, J. A. M. A. **111**:584 (Aug. 13) 1938.

158. Reynolds, S. M.: Science **87**:537 (June 10) 1938.

159. Code, C. F.: J. Physiol. **90**:349 (Aug.) 1937.

changes are the final common pathway for many etiologic agents. Probably more than one factor is operative in most cases; however, in my opinion, antigen-antibody reactions are not the cause of most allergic lesions of the eye. Many factors are of endogenous origin, and failure of homeostatic mechanisms adequately explains many cases.

A problem which requires further study is this: Why does acute iritis occur in one person, acute choroiditis in a second and episcleritis in a third, while in still others acute retrobulbar neuritis, herpes, acute glaucoma, paralysis of an ocular muscle or acute closure of the central retinal artery or one of its branches develops, with approximately the same etiologic background for all? Except for the fact that there seems to be a definite age incidence for the occurrence of these lesions, nothing further can be stated as to why these lesions develop.

I believe that allergy is a manifestation of hypersensitive vascular units and that "shock" arterioles and capillaries, rather than "shock tissues," are the basis of allergic lesions.

The treatment of ocular allergy with vasodilator substances has been productive of excellent results, both in my cases and in the cases reported by many other clinicians. Such treatment is nonspecific as regards the cause but specific as regards the pathophysiologic basis of these lesions.

CONCLUSIONS

The body as a whole probably has only a few simple ways of reacting to a variety of insults, whether they are chemical, bacterial, climatic or traumatic.

Ocular allergy is not a disease *sui generis,* but one which can be interpreted and investigated as a manifestation of a "morbid" physiologic state. Lesions differ in degree rather than in kind when the same tissue is involved. In different tissues the same basic pathologic process may cause superficially different lesions because of the structure of the tissue involved and its effect on the development of the lesion.

Allergy of the ocular tissues can be interpreted as a manifestation of localized vascular dysfunction.

This vascular dysfunction causes areas of localized tissue anoxia. Anoxemia is not usually, or necessarily, present.

Vasodilator therapy, which acts by relieving the tissue anoxia, seems to be of value in the treatment of the allergic lesions of the eye which have been discussed in this article. This treatment is based on the pathologic physiology of the lesions.

Further study is necessary to confirm or deny the opinions stated and the conclusions drawn from a study of the literature and from clinical research on patients.

258 Genesee Street.

EXPERIMENTAL STUDIES ON THE BLOOD-AQUEOUS BARRIER

I. New Electrophotometric Method of Measuring the Concentration of Fluorescein in the Aqueous

FREDERICK W. STOCKER, M.D.
DURHAM, N. C.

THE exchange of water and other substances between the blood and the contents of the eye is not only an interesting physiologic and biochemical phenomenon but also a vital factor for the maintenance of the intraocular pressure on a certain level. In order to understand better the abnormal variations of the intraocular pressure, one should know as much as possible about the normal mechanism of the exchange of fluid between the blood and the eye, the rate of inflow of the fluid and how this rate may be changed under various conditions. Several attempts have been made to supply the blood with a tracer substance, the presence of which could be demonstrated in the aqueous after having passed through the blood-aqueous barrier. As far back as 1882 Paul Ehrlich [1] discovered that fluorescein injected into a rabbit's vein will appear in the aqueous after a comparatively short time. However, a controversy developed with regard to whether the mode of diffusion of fluorescein through the capillary walls really revealed the secret of how the aqueous originated and by which route and in what time it enters and leaves the eye. Whereas Ehrlich was inclined to believe that the fluorescein test would be useful for the advance of knowledge of the origin and circulation of the aqueous, Leber [2] was critical of its usefulness. He pointed out that by using an extremely highly diffusible substance, such as fluorescein, one would not get conclusive information on the circulation of the solvent, and therefore not of the aqueous itself. Wessely [3] found that there was a great difference between the concentration of fluorescein in the blood, on one side, and in the aqueous, on the other, inasmuch

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Dr. W. A. Perlzweig, Professor of Biochemistry, gave me the use of the photofluorometer and other facilities of the Department of Biochemistry.

1. Ehrlich, P.: Ueber provocierte Fluorescenzerscheinungen am Auge, Deutsche med. Wchnschr. **8**:21, 35 and 54, 1882.

2. Leber, T., cited by Hertel.[5]

3. Wessely, K.: Der Flüssigkeits-und Stoffwechsel des Auges mit besonderer Berüchsichtigung seiner Beziehungen zu allgemein physiologischen und biologischen Fragen, Ergebn. d. Physiol. **4**:626, 1905.

as the aqueous always contained considerably less fluorescein than the blood. He concluded that an elective function of the ciliary epithelium, absorbing and secreting the fluorescein, was responsible for these differences. Consequently, he supported the theory that the aqueous did not originate by simple diffusion through the capillary walls but was the product of a definite secretory process of the ciliary epithelium. On the other hand, Yoshida [4] proved that when the blood serum is passed through a protein-restraining filter the filtrate contains approximately the same concentration of fluorescein as the aqueous, and Hertel [5] demonstrated that with an increase of blood proteins by intravenous injection of gelatin the diffusion of fluorescein into the anterior chamber was delayed. De Haan and Van Creveld [6] demonstrated that, also, the differences in concentration of glucose in the blood and in the aqueous have to be explained by the absorption of large amounts of glucose by the blood proteins.

After a careful evaluation of these, and a great number of other, studies, which I may be permitted to pass over in the interest of economy of space, it seems that the fluorescein test is a useful method for studying the production and circulation of the aqueous. However, when I attempted to use fluorescein for experimental studies of possible changes in the relations between blood and aqueous under the influence of certain substances, I strongly felt the lack of an accurate way of recording the concentration of fluorescein in the aqueous. Clinical observation, no matter whether daylight ultraviolet light or the beam of the slit lamp was used, proved to be unsatisfactory. When several observers followed the same experiment, the opinion as to the first appearance of fluorescein in the anterior chamber and as to the intensity of fluorescein varied within considerable limits. Some authors, among them Yoshida,[4] used a colorimetric test by which the aqueous aspirated from the anterior chamber was compared with standard solutions; but my experience was that even so there remained a great deal of inaccuracy and arbitrary judgment. I even feel that some of the results reported by various experimenters and clinical investigators lack the power of conviction because of these shortcomings.

Recently, other substances were used as tracers instead of fluorescein. Kinsey, Grant and Cogan [7] used heavy water, which was given to rabbits

4. Yoshida, Y.: Ueber Wechselbeziehungen zwischen Blut und Kammerwasser, Arch. f. Augenh. **100**:470, 1929.

5. Hertel, E.: Ueber die Bedeutung der Ehrlichschen Fluoreszeinversuche, Arch. f. Augenh. **100-101**:460, 1929.

6. de Haan, J., and van Creveld, S.: Ueber die Wechselbeziehungen zwischen Blutplasma und Gewebsflüssigkeiten, insbesondere Kammerwasser und Cerebrospinalflüssigkeit, Biochem. Ztschr. **123**:190, 1921.

7. Kinsey, V. E.; Grant, M., and Cogan, D. G.: Water Movement and the Eye, Arch. Ophth. **27**:242 (Feb.) 1942.

by intraperitoneal injections and could be recollected quantitatively in the aqueous. An especially ingenious method, which appeals to the mind of the age of atomic fission, was devised by Kinsey, Grant, Cogan, Livingood and Curtis.[8] They used radioactive isotopes of sodium, chloride and phosphorus as tracer substances. However, the procedure seems to be rather complicated, as these substances have to be prepared in the cyclotron by being bombarded with deuterons. Furthermore, it is not yet clear to what extent the migration of these substances really reveals the movement of water through the blood-aqueous barrier. Also, considerable differences in the rate of accumulation in the aqueous of chloride, sodium and phosphorus were reported. In spite of these interesting experiments, I still believe that the fluorescein test would give the necessary information if a more accurate method of measuring the amount of fluorescein in the aqueous were available.

The first part of this paper will be devoted to the description of a new method which I developed for the measuring of fluorescein of the aqueous and its application to experimental work. The instrument used was the Model 12, Electronic-Photofluorometer.[9] This is an improved apparatus designed to insure strict linearity between fluorescent intensity and meter readings. It is widely used for measurments of concentration of certain vitamins. Two sets of filters are furnished, B_1 and PC_1 for measurements of thiamine and B_2 and PC_2 for measurements of riboflavin and porphyrin. Preliminary experiments revealed that for measuring fluorescein the yellow filters, B_2 and PC_2, are more suitable than the blue filters, B_1 and PC_1. It was found that 1:8,000,000 dilution of sodium fluorescein was adequate as a standard in order to set the instrument. Although the reading appeared to be greatly reduced when the p_H of a solution was lowered below about 5, it also could be demonstrated that between p_H 7 and p_H 9 no appreciable difference was noted. As the p_H of the aqueous proved to be around 7.8, it is permissible to neglect the p_H when examining this fluid. (Duke-Elder[10] stated that the p_H of the aqueous of man is 7.5 to 77.)

EXPERIMENTS

A solution containing 0.05 Gm. of sodium fluorescein per kilogram of body weight was injected into the ear vein of an albino rabbit. To accomplish this, 0.50 cc. of a 10 per cent solution, or 0.25 cc. of a 20 per cent solution, per kilogram was used. About twenty seconds after the injection the conjunctiva and the lid

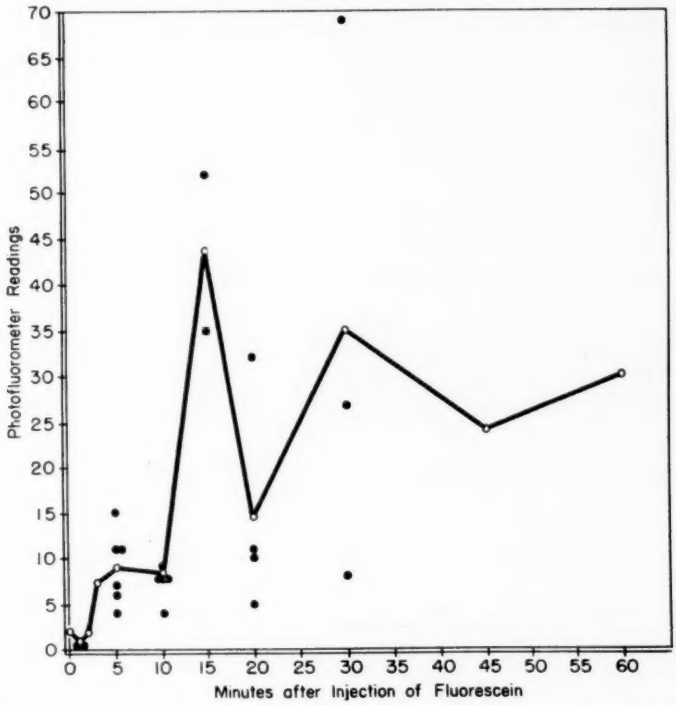
8. Kinsey, V. E.; Grant, W. M.; Cogan, D. G.; Livingood, J. J., and Curtis, B. R.: Sodium, Chloride and Phosphorus Movement and the Eye, Arch. Ophth. **27**:1126 (June) 1942.

9. Manufactured by the Colman Co., Inc., Maywood, Ill.

10. Duke-Elder, W. S.: The Nature of the Intraocular Fluids, British Journal of Ophthalmology Monograph Supplement 3, London, George Pulman and Sons, Ltd., 1927.

margins showed a definite yellow coloration. The cornea was anesthetized with a few drops of 2 per cent cocaine, and 0.20 cc. of aqueous was aspirated from the anterior chamber at various times after injection.

Each eye of an animal, of course, could be used only once during one session. It is known that the so-called second aqueous differs very much from the first one and does not show any longer the concentration of fluorescein found in the serum filtrate, called free fluorescein, but has the concentration of the serum itself, owing to its increased protein content. The same animal was not used again for at least seven days. The specimen of aqueous then was diluted with 8 cc. of distilled water in order to get the minimum quantity of fluid required for the readings of the photofluorometer. After the instrument had been set at 100



Fluorescence of aqueous of rabbits after intravenous injection of fluorescein sodium. Individual readings are indicated by solid dots; average readings, by hollow dots.

with a standard solution of 1 : 8,000,000 of the sodium fluorescein, always freshly prepared the very day of the experiment, the diluted specimens of aqueous were examined and the readings recorded.

In the accompanying graph the results of thirty such readings are plotted.

The normal aqueous shows a slight fluorescence of its own, and up to two minutes after the injection of fluorescein no appreciable change in fluorescence was recorded. From three to ten minutes after the injection a definite increase in fluorescence appeared. Individual readings

during this period showed only a moderate discrepancy and were most uniform in about ten minutes. At the end of fifteen minutes and later the readings became rather irregular, though much increased on the average. This peculiar phenomenon is still awaiting a definite explanation. Pending further investigation, I am inclined to believe that it has something to do with the process of absorption of fluorescein by the serum proteins and its release at a certain later time. Just how this mechanism is regulated I am unable to demonstrate at present. However, for the purpose of this study, the period after ten minutes is rather irrelevant, the interval from three to ten minutes being the "critical" one, as will be seen in the second part of this paper.

SUMMARY

1. A new method of recording fluorescence of the aqueous after intravenous injection of sodium fluorescein, using the Colman photofluorometer, is described.

2. It is demonstrated that the diffusion of fluorescein from the blood into the aqueous of rabbits takes a fairly regular course between three and ten minutes after the injection, after which time it becomes irregularly increased.

In the second part of this study it will be demonstrated, with the method here described, how the rate of diffusion of fluorescein from the blood into the aqueous may be altered through the influence of various substances.

Duke University School of Medicine.

Clinical Notes

A RULER FOR MEASUREMENT OF VISUAL FIELDS ON THE TANGENT SCREEN

LOREN P. GUY, M.D., NEW YORK

A TANGENT screen for charting visual fields is difficult to make and, if purchased, is expensive. Plotting the measurements on a surface and painting or sewing them on requires skill in mathematics as well as manual dexterity. When completed, the marks of the measurements are usually for one distance only—1,000, 2,000 or 3,000 mm.—and are set at one height. As it is often desirable to take fields with the tangent screen at more than one distance, it is an advantage to have available the measurements for 1,000, 2,000 and 3,000 mm. Tangent screens can be made so that they may be elevated or lowered to suit the height of the individual patient, but this adds to an already complicated and expensive procedure. These difficulties and shortcomings may be responsible for neglect in utilizing the valuable diagnostic and prognostic aid which tangent screens offer.

In order to obtain a ready method of charting visual fields with a tangent surface, a ruler was designed. It is simply a triangular ruler, measuring 1,500 by 20 mm. On one surface are recorded the measurements at 5 degree intervals at 1,000 mm.; on another the measurements at 5 degree intervals at 2,000 mm., and on the third surface, the measurements at 3,000 mm. A schematic diagram showing the measurements between the intervals is illustrated in figure 1. The tangent screen on which the fields are to be charted is left blank except for an object for the patient's eye to fix on. This has an advantage over screens that are marked, because markings divert the attention of some patients.

To record and chart the visual fields on the tangent screen, the patient is placed at the desired distance, usually 1,000, 2,000 or 3,000 mm. from a tangent surface. This surface may be a cloth screen, a blackboard, a wall or any suitable flat surface. An object, such as a white pin or a chalk mark, for the patient's eye to fix on is placed directly in front of the patient's eye. Then the fields are plotted with test objects of the same type and size as are used in a marked tangent screen, and the same procedure is followed. When the fields are plotted, the ruler is used to chart them on a suitable record. Figure 2 illustrates how this is done. Meridian lines are hardly needed for an ophthalmologist, since he is accustomed to dealing with the various meridians in refractions.

This ruler[1] has been used for several years and has been found to be satisfactory. It has been presented for criticism at a clinical conference of the New York Eye and Ear Infirmary and before the Section on Ophthalmology of the New York Academy of Medicine. It is felt that this ruler offers an accurate, easily constructed and inexpensive means of measuring for recording plotted tangent surface fields.

40 East Sixty-Second Street.

1. Clairmont & Nichols, 515 Madison Avenue, New York, have made some of these rulers.

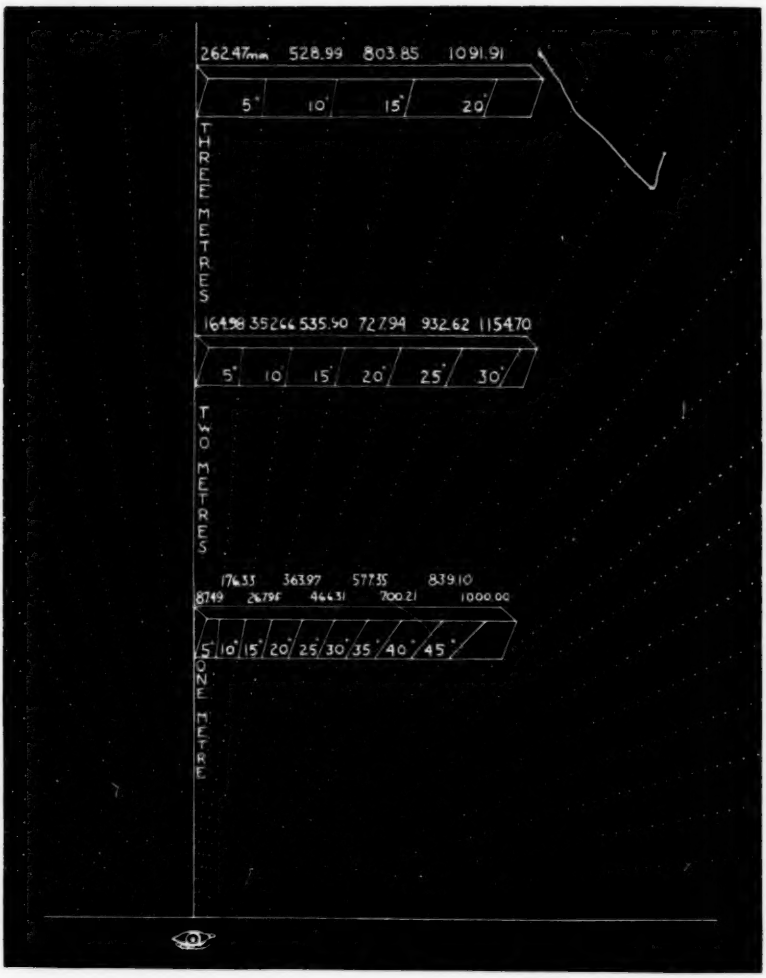


Fig. 1.—Diagram showing scheme of the ruler and measurements.

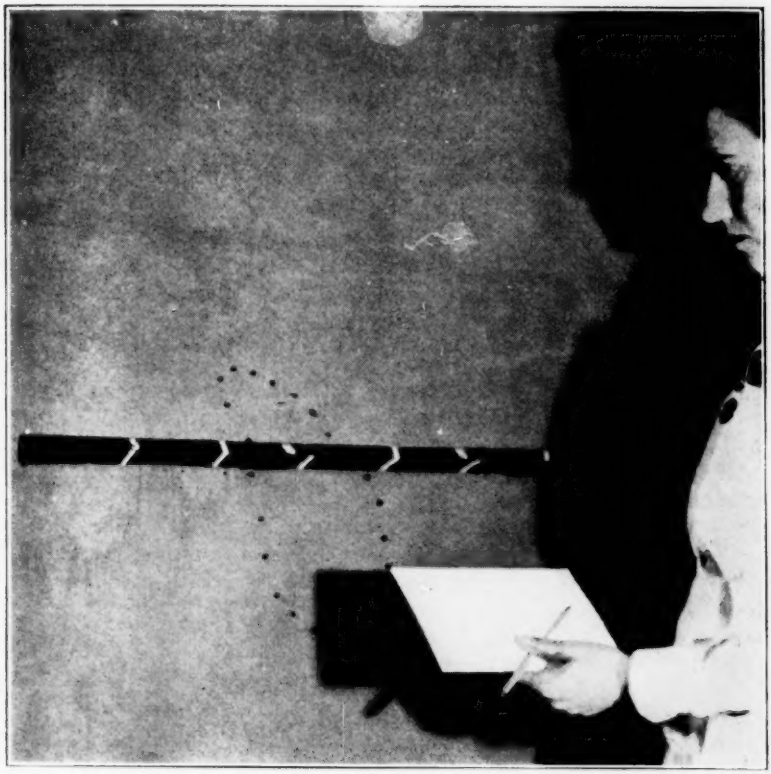


Fig. 2.—The ruler being used to record fields charted on the tangent field.

Correspondence

ALLERGIC REACTION TO SCOTCH TAPE

To the Editor:—In the February 1941 issue of the ARCHIVES is an article in the section on "Clinical Notes" entitled "A Better Adhesive Tape for Use After Surgical Treatment of the Eye." The author rightly states that Scotch tape is a preferable substitute for adhesive tape treated with zinc oxide in applying ophthalmic dressings. To further the use of this new tape in ophthalmic dressings, he emphasized the apparent freedom from allergic dermatitic reactions to Scotch tape even in patients experiencing cutaneous sensitivity to adhesive tape treated with zinc oxide.

Recently, after some eight years of experience with Scotch tape and with similar tapes, I witnessed a severe allergic reaction following bandaging of both eyes. The weeping, edematous and hyperemic reaction become so extensive that dressings had to be removed and the much swollen face had to be treated as a burn. The eye which had been operated on reacted with an exudative reaction. There was extensive regional lymphadenopathy.

Investigation disclosed that the patient was also highly sensitive to adhesive tape treated with zinc oxide and to two types of Scotch tape. The manufacturers presented the following analysis of pressure-sensitive tapes as containing an elastomeric component (normally some type of rubber), an adhesive component (normally a resin derivative) and an antioxidant (normally often a phenol derivative). The elastomeric component in this case was probably responsible for the allergic reaction.

Prior to the war natural rubber was used exclusively. In the early stages of the war various substitutes were used, including polyisobutylene. During the later stages of the war synthetic rubber of the GR-S type was concentrated on. More recently some natural rubber has again become available and tapes have been made of mixtures of synthetic and natural rubber. It is thought that there is more danger of allergic reactions to natural rubber than to synthetic rubber.

The difficulties encountered in treating the sequelae of this allergic reaction accentuate the necessity to inquire of all patients as to any previous reactions to tapes and to give the patch test to elective surgical patients at the time of their first office visit.

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400 Norman Bridge Road (6).

REQUESTS FOR COPIES OF WARTIME ISSUES OF AMERICAN JOURNALS FOR OPHTHALMOLOGISTS ABROAD

To the Editor:—Several months ago a notice was placed in the *American Journal of Ophthalmology* and in the ARCHIVES stating that ophthalmologists abroad would welcome the wartime issues of the American journals which were not otherwise being saved. As a result sets of journals have been sent to Europe, China and the Philippines, and grateful acknowledgments have, in most instances, been received. The expenses

of shipment have been borne in some cases by the senders at their request and in other cases by a fund set up for this purpose through the generosity of Mrs. Elizabeth Proctor.

We should appreciate hearing from any others who may wish to dispose of their wartime issues, and, as the requests come in, we shall pass them on to the prospective donors together with instructions regarding the shipments. All correspondence should be addressed to Miss Jeannette Loessl, Howe Library of Ophthalmology, 243 Charles Street, Boston 14.

DAVID G. COGAN, M.D., BOSTON.

243 Charles Street (14).

DIISOPROPYL FLUOROPHOSPHATE ("DFP") IN TREATMENT OF GLAUCOMA

To the Editor:—The advent of diisopropyl fluorophosphate ("DFP") in ophthalmology probably marks a significant advance in the medical control of glaucoma. The disconcerting ciliary spasm and after-blur, however, will limit its field to cases of glaucoma inadequately controlled by the previously known antiglaucomatous drugs, as intimated by Leopold and Comroe in their introductory article (Use of Diisopropyl Fluorophosphate in the Treatment of Glaucoma, ARCH. OPHTH. **36:** 1 [July] 1946.

About five months ago Dr. Leopold graciously sent me a generous supply of "DFP," which my associates and I have been using in selected cases at Cook County Hospital and at the Veterans Administration Facility, Hines, Ill., as well as in private practice. The optimum results have generally been obtained with a 0.05 per cent solution administered morning and evening. Stronger solutions cause more discomfort, and in cases in which the 0.05 per cent concentration has failed to lower the tension sufficiently, stronger solutions have not been more effective. It is also possible that a too intense ciliary spasm, or the pain this occasions, may have an adverse effect. I recall an elderly patient with acute glaucoma who had achieved comfort, with a tension of 35 mm., with a 0.25 per cent solution of physostigmine salicylate; after the substitution of 2 per cent physostigmine nitrate, at the suggestion of a consultant, acute pain followed, and the tension rose to 65 mm. Though the miosis from "DFP" lasts several days, the intraocular tension usually reaches its lowest in twelve to fifteen hours, so that in the average case instillations morning and night constitute the logical treatment. However, some patients with moderately elevated tensions required but one instillation daily. Other patients who at first reacted brilliantly later failed to respond even with more frequent use and with stronger solutions.

In most cases of secondary glaucoma, including uveitis, rubeosis iridis and occlusion of the central retinal vein, use of "DFP" proved futile. But in 2 cases of morgagnian cataract in which pilocarpine had lowered the tension from 70 to 30 mm., "DFP," instilled once daily, reduced the tension to 14 mm. The cataract operation was then done, with uneventful recovery. Of 3 cases of glaucoma following cataract extraction in which pilocarpine and physostigmine had been ineffective, "DFP" successfully lowered the tension in 2. In the third case a tension of 62 mm. had also persisted after a previous cyclodialysis.

The very high tensions may respond only slightly to use of "DFP." A woman with chronic simple glaucoma and a tension of 101 mm. in each eye was treated with physostigmine and pilocarpine without any change in her condition. With use of "DFP" (0.05 per cent four times a day for five days) the tension became only 86 mm. in the right eye and 101 mm. in the left eye.

In normal eyes atropine cycloplegia, whether produced by instillation or by internal medication, may be more than counteracted by 0.1 per cent "DFP," and in 2 instances homatropine had to be instilled to reduce the persisting ciliary spasm and photophobia. But for relief of glaucoma precipitated by atropine the drug has only slight value. A diabetic patient with amblyopia of the left eye from hemorrhages in the vitreous was treated with atropine for a corneal ulcer in this eye. Though the ulcer healed, the eye became excruciatingly painful. The tension then taken was 45 mm. in the right eye and 118 mm. in the left eye. Three days later, after use of "DFP," the tension was 17 mm. in the right eye and 86 mm. in the left eye, and the pupillary diameters were 1.5 and 4 mm., respectively. The pain in the left eye was then relieved by a retrobulbar injection of 0.5 cc. of 60 per cent alcohol and use of "DFP" was continued, but during ten days of observation the pupil contracted no further and the tension did not decrease below 75 mm.

We have found that the prompt and persisting miosis produced by one application of 0.05 per cent "DFP" at the conclusion of operation makes this drug the miotic of choice in the intracapsular extraction of cataract through a round pupil and in cyclodialysis.

JAMES E. LEBENSOHN, M. D., CHICAGO.

4010 Madison Street.

News and Notes

EDITED BY DR. W. L. BENEDICT

SOCIETY NEWS

Philippine Ophthalmological and Otolaryngological Society.—The Philippine Ophthalmological and Otolaryngological Society has been formed, and the inaugural meeting was held on Jan. 26, 1946, at the Gauzón Memorial Hall, Philippine General Hospital, Manila.

The following officers were elected: president, Antonio S. Fernando, M.D.; vice-president, Edmundo Reyes, M.D.; secretary-treasurer, Jose N. Cruz, M.D.; directors, Germiniano de Ocampo, M.D.; Tomas Hano, M.D.; Jesus Eusebio, M.D., and Gregorio Färrales, M.D.

Meetings will be held in January, March, May, July, September and November.

GENERAL NEWS

Twentieth Annual Spring Graduate Course in Ophthalmology and Otolaryngology.—The annual spring graduate course in ophthalmology and otolaryngology will be held at the Gill Memorial Eye, Ear and Throat Hospital, Roanoke, Va., April 7 to 12, 1947.

Abstracts from Current Literature

EDITED BY DR. WILLIAM ZENTMAYER

Cornea and Sclera

UNUSUAL TYPE OF CORNEAL OPACITIES. J. W. HENDERSON and D. R. GILLESPIE, Am. J. Ophth. **28:** 1236 (Nov.) 1945.

Henderson and Gillespie report 8 cases of temporarily blurred vision due to fine brownish opacities in the cornea. Microscopic examination of the eye of a patient who died of hepatitis showed that these opacities were scattered along the posterior endothelial layer of the cornea. No evidence of systemic disease or avitaminosis was found.

W. S. REESE.

A CASE OF MUSTARD GAS KERATITIS TREATED WITH CURETTAGE OF THE CORNEA FOR THE REMOVAL OF A BAND-SHAPED CRYSTALLINE DEPOSIT. H. NEAME, Brit. J. Ophth. **29:**102 (Feb.) 1945.

Neame reports this case because it has become customary to regard cases of severe mustard gas (dichloroethyl sulfide) keratitis unsuitable for operation because of the liability to recurring ulceration.

A man aged 56 was fitted with contact lenses on account of progressive deterioration of vision. Visual acuity in the left eye was 3/60, owing to a transverse band on the cornea extending across and below the pupillary area, composed of a superficial deposit of crystalline appearance and completely obstructing the vision. After curettage of the opacity vision gradually increased until, two years later, it was 6/36 with a contact glass.

W. ZENTMAYER.

General

A REVIEW OF EYE DISEASE IN CENTRAL CHINA. G. H. PEARSON, Brit. J. Ophth. **29:**260 (May) 1945.

The basis of this review is experience during a residence of twenty-four years in Shaoyang, Hunan, Free China, in which Pearson's main interest has been ophthalmology. The great bulk of the cases has always been those of conjunctival infections and their sequelae. Between 1929 and 1942, 1,341 inpatients were treated for trachoma; 1,027 operations were performed for entropion and 51 operations for cataract. The treatment of diseases of the fundus and the prescription of glasses have assumed a minor role, owing to social conditions. The call for properly adjusted glasses is increasing, and it is now possible to get glasses ground locally by Chinese firms.

The cases of trachoma are separated into cases of the early form, with only rudimentary formation of follicles and with, as yet, no macroscopic pannus formation; cases of fully developed trachoma; cases of the cicatricial stage, in which the follicles have mostly disappeared and scar

tissue has taken their place, and cases of the "hard type of trachoma," in which the fibrous tissue takes on a hard, nodular condition and when fully developed looks like a tessellated pavement (probably the "spring catarrh" described in textbooks, but in Hunan it definitely belongs to the trachoma family), and cases of a late degenerative condition, the formation of a plasmoma. In China a pterygium often is a late complication of the multiple irritations of trachoma, though it may in theory occur without trachoma.

After trying out most of the operations for entropion, the author now uses almost uniformly the Hotz operation.

Trachoma with its sequelae is one of the greatest causes of ultimate blindness in Free China.

W. ZENTMAYER.

USE OF MIXTURE OF ENCODAL, SCOPOLAMINE AND EPHETONIN IN OPHTHALMOLOGY. POYALES, Arch. Soc. oftal. hispano-am. **4:** 365 (May-June) 1944.

Poyales uses this combination of drugs to induce twilight sleep for certain operative procedures in ophthalmology. Encodal is a codeine derivative (dehydrooxidocodeine), a substitute for morphine in the morphine-scopolamine mixture. It is more analgesic and less toxic, although more likely than morphine to produce habit formation. To this mixture ephedrine or Ephetonin (an isomer of ephedrine) is added as a stimulant to the respiratory and cardiac centers, to counteract the depressing action of scopalamine.

The combination is used in cases of acute glaucoma while the proper time for surgical intervention is awaited and also as a preliminary to probable painful operations, such as dacryocystorhinostomy, exenterations for panophthalmitis and retinal detachment.

H. F. CARRASQUILLO.

General Diseases

OCULAR COMPLICATIONS OF CERTAIN TROPICAL DISEASES. M. J. REEH, Am. J. Ophth. **28:**958 (Sept.) 1945.

An abstract of the author's summary follows.

After World War II physicians may encounter tropical diseases which are rare or unknown in the United States. These will be found in men who have served in the armed forces overseas or among persons who will travel extensively because of the vast postwar development of highways and air lines. Any one ophthalmologist will see an extremely limited number of cases, however. Fortunately, ocular complications are found to occur with only a few of the many tropical diseases.

Malaria is believed to be one of the causes of dendritic keratitis. At the present time clinical observations are not conclusive. The true etiologic basis is still vague. Other ocular complications of malaria are rare. The more serious complications result from the administration of quinine to sensitive persons.

African trypanosomiasis will probably always be extremely rare in the United States; however, the final outcome in untreated patients is so disastrous that it is well for all physicians to be on the alert.

Filarial diseases are extremely common in various parts of the world. Despite the widespread existence of Wuchereria bancrofti, cases of entrance of this worm into the globe are rare. The adult Loa loa lives in the body for many years. It wanders freely about in connective tissue, frequently appearing beneath the skin of the lids or the conjunctiva—hence the old name Filaria oculi. It does not tend to enter the globe itself, however. Onchocerca volvulus, on the other hand, is destructive to the eye. The microfilarias enter the layers and chambers of the eye readily, producing inflammation which not infrequently results in blindness. Onchocerciasis may prove to be more troublesome in the future because of increased travel into areas of Mexico and Guatemala where the disease is endemic.

Reeh reaches the following conclusions: Certain tropical diseases produce ocular complications. Such complications may be improperly evaluated and inadequately treated because the causative disease is not recognized.

W. ZENTMAYER.

ROLE OF FOCAL INFECTION IN OPHTHALMIC DISEASE. J. PEREIRA GOMES, Arq. brasil. de oftal. **7:** 201 (Dec.) 1944.

A historical summary of the subject is presented. A personal observation on a patient aged 22, who was blind in the right eye, is given. After removal of the upper row of teeth, all of which were infected, vision returned to 9/10. The author states that, in his opinion, the upper teeth when infected can cause more damage than the lower. When there is suspicion of focal infection, other probable foci should be sought for, and the patient should be requested to submit to laboratory examinations. In the case of dental foci a close collaboration between dentist and ophthalmologist is desirable. The duty of an ophthalmologist, however, lies in removing every possible cause of the ocular lesion, for, although certain foci may not be entirely responsible for the ocular diseases, their removal will benefit the patient's general health.

M. E. ALVARO.

Hygiene, Sociology, Education and History

READING DISABILITY: A PEDIATRIC PROBLEM. T. H. WOLF, Journal-Lancet **65:** 184 (May) 1945.

Wolf shows that disability in reading may play a part in the physical complaints and emotional tensions found in school children, particularly in those 9 to 10 years of age or older. From the fourth, fifth and sixth grades on, the ability to read assumes an increasingly important part in nearly every school subject. A youngster unable to compete with his classmates because he cannot read finds himself at a disadvantage, and repeated failure results in unhappiness, for which he may try to compensate in various ways. He may present a behavior problem, becoming sullen and negativistic toward his teacher and classmates. He may become the bully or withdraw from contacts with the group. On the other hand, he may have bizarre physical complaints, varying from mild headaches to severe digestive disturbances, fainting spells or convulsive seizures. He may manifest both emotional and physical symptoms. A case recently encountered in the pediatric outpatient

department of the University of Minnesota Hospitals illustrates the point. A frequent error of parents and teachers is to think of the child as dull and stupid. Measured intelligence and rapid progress in school after remedial treatment have proved otherwise. Uncorrected conditions of the eye or ear may be responsible for the reading difficulties. The physician should look for muscular imbalance, which may cause a lack of fusion of visual images. Some children need additional corrective training of ocular muscles. Islands of deafness may be recognized. Other factors that play a part in reading disability are inadequate instruction, emotional problems and cerebral factors. The theory that the causative factor was left handedness, a mixed eye-hand dominance in the cerebral hemispheres, has been open to serious question and criticism. Most, if not all, of the difficulties can be relieved with proper guidance.

J. A. M. A. (W. ZENTMAYER).

Injuries

CHRONIC POSTTRAUMATIC SYNDROMES LEADING TO ENUCLEATION. B. A. KLIEN, Am. J. Ophth. **28:** 1193 (Nov.) 1945.

Among the inflammatory and other post-traumatic chronic conditions that led to enucleation of the 77 eyes reported on in this series, nonspecific infiltrating iridocyclitis, far from being the most frequent condition encountered, occurred in only 17 eyes, or 22 per cent. More frequent was chronic septic endophthalmitis, present in 20 eyes, or 26 per cent. Four other conditions accounted for more than one third of all the enucleations; namely, epithelial implants (12 per cent) and chronic hemophthalmos, extensive contusion necrosis and late toxic iritis after long-standing retinal detachment (8 per cent each). Endogenous iridocyclitis occurred in 5 per cent of the eyes, and some rarer conditions were present in a total of 3 per cent. Sympathetic ophthalmia itself occurred in only 6 eyes, or 8 per cent (less than 3 per cent of the 219 penetrating injuries).

There was no evidence in any of the eyes in this series to suggest that they could have been saved.

W. S. REESE.

TREATMENT OF PERFORATING WOUNDS AND BURNS OF THE EYE WITH LYSOZYME. E. CHECHIK-KININA, Vestnik oftal. **24:** 42, 1945.

The titer of the lysozyme of the tears was determined in 25 eyes with penetrating injuries, as well as in normal eyes. The lysozyme content was lowered considerably in 23 eyes, as compared with the titer of the tears of normal eyes. The infection was in inverse proportion to the lysozyme content; i. e., the higher the lysozyme content, the lower was the number of ocular infections.

Lysozyme was used in the form of instillations, ionization and injections into the anterior chamber in 54 patients with perforating wounds of the eye. This prophylactic treatment gave good results, as only 12.7 per cent of the eyes were lost.

Lysozyme was also used in treatment of burns of 31 eyes; in only 3 eyes with very severe burns (necrosis of the tissues) was the lysozyme therapy not effective.

Experimental tests on 10 rabbits verified the beneficial effect of lysozyme in treatment of burns of the eye.

The following conclusions are drawn. The titer of lysozyme as a rule is lowered in cases of perforating ocular injuries.

The number of infections associated with perforating injuries of the eye is in direct ratio to the lowered titer of lysozyme of the tears.

The titer of the lysozyme of the tears has a definite prognostic value.

The treatment of perforating injuries of the eye with lysozyme gave favorable results.

The treatment of mild and severe burns of the eye with lysozyme was quite effective. Only in 3 eyes with extremely severe burns did the treatment give negative results.

Experimental work on rabbits confirmed the value of lysozyme in burns of the eyes.

O. SITCHEVSKA.

Lacrimal Apparatus

RHINOSTOMY AND ITS INDICATIONS. E. M. IVANOVA, Vestnik oftal. **24:** 12, 1945.

This article is a tribute to the late professor Averbach, who was the pioneer in Soviet Russia in the use of dacryocystorhinostomy. From 1926 to date there were performed 6,000 rhinostomies. Averbach stated that a large hole in the nasal bone (1.5 by 1.5 cm.) is the most important factor in obtaining the best end results. The sutures in the mucous membrane are of secondary importance.

Averbach expressed his belief that there are hardly any contraindications to this operation. It is especially indicated in cases of recurrent phlegmon of the sac, as the dacryocystitis and the phlegmon are done away with. It is not difficult to perform the operation on aged people. Because of the fragility of the bone, it is easy to make the opening in the bone.

Successful results were obtained in 97 per cent of cases. The unsuccessful results in 3 per cent were due either to too small an opening or to an incorrect position at the opening in the bone.

O. SITCHEVSKA.

Methods of Examination

A SIMPLE DEVICE FOR TESTING DIPLOPIA. I. C. MICHAELSON, Brit. J. Ophth. **29:** 376 (July) 1945.

The device consists of a cap with an arrow-shaped perforation; the opposite inner wall is painted white to reflect the internal light. The cap fits over the lamp end of the ophthalmoscope. A 10 inch (25.4 cm.) pendant string, weighted at its end, is marked into inches with small pieces of metal. The distance between the false and the true image can be found by asking the patient to touch the arrow and then point to the false image. The distance between the arrow and the patient's finger is measured on the string. The degree of tilting of the false image can be found by tilting the handle of the lamp until the false image is erect and then noting by touch the angle between the handle and the dependent string.

The article is illustrated.

W. ZENTMAYER.

Neurology

HYSTERIA IN OPHTHALMOLOGY: EXPERIENCES WITH NEW ZEALAND TROOPS IN THE MIDDLE EAST. H. COVERDALE, Brit. J. Ophth. **29:** 120 (March) 1945.

Among 58,927 troops which constituted the New Zealand expeditionary force to the Middle East up to the end of November 1943, 95 had a condition diagnosed as hysteria, in 50 of whom it was considered severe and in 45 mild. The average age was 30 years. Of the 95 men, 62 had not been in action with the division, while the remaining 33 had been with the division in the field, though not necessarily in action in the face of the enemy; very few had been sent back to base because the disability had occurred during combat. The majority had paraded sick, and the diagnosis had been made soon after their arrival in Egypt. The most interesting fact to emerge from the clinical examination of these men was that a high proportion had some preexisting ocular defect, dating in most cases from childhood. It may be that such ocular disabilities tend to make men susceptible to hysteria or, on the other hand, that in persons who are prone to hysteria from heredity, environment or other causes, the disability tends to appear in that organ which the man, consciously or unconsciously, believes to be weak.

W. ZENTMAYER.

AMBLYOPIA WITH HYDROCEPHALUS. K. N. PRADHAN, Indian J. Ophth. **6:** 11 (April) 1945.

In a case of acute hydrocephalus, possibly of malarial or filarial origin, in an infant 3 weeks old, there was in the right eye a gray-white atrophy of the optic nerve, and in the left eye congestion of the disk. Two years later there was marked atrophy of the optic nerve in both eyes, though the child could recognize people at 20 feet (6 meters). As modern treatment will save an increasing number of patients with serous meningitis, the problem of preserving the vision of such patients confronts one.

W. ZENTMAYER.

The Pupil

SEGMENTAL MOVEMENT OF THE PUPIL. IAN S. MCGREGOR, Brit. M. J. **1:** 629 (May 5) 1945.

Segmental movement, or twitch, at the pupillary margin was first described by Sattler, in 1911. It is seen in the pupil which has no normal reaction to light or in which the response to light is much diminished. Sometimes only a single twitch is apparent; in other cases a similar twitch may appear at another place in the pupillary margin. The worm contraction, or undulate contraction, of the pupillary border is much less common. These changes are readily observed with the use of a low power magnifying loupe or microscope. Patients with partial loss of field after head injury and patients with glaucoma showed no segmental movement. A number of patients were examined in order to determine whether the sign had any localizing value. These included persons with syphilitic atrophy of the optic nerve, post-

traumatic atrophy of the optic nerve, Leber's disease, blindness due to quinine (1 patient), retrobulbar neuritis, and unilateral Adie's pupil (2 patients).

This disturbance is associated with sufficiently severe disorders of the afferent or efferent nerve paths to the sphincter of the pupil. It is not seen in the contracted pupil. It may be due to diminished conduction in the nerve paths to the sphincter pupillae, or there may be a pathologic variation or inequality of flux within the nerve plexus.

The author concludes that "the sign, so far as this short investigation will allow us to conclude, will not appear to have any localizing value; it is a fibrillation of the pupil resulting from impaired integrity of the nervous arc of the sphincter pupillae occurring at any part of the arc."

ARNOLD KNAPP.

Refraction and Accommodation

RELATIONSHIP BETWEEN VISUAL ACUITY AND REFRACTIVE ERROR IN MYOPIA. J. S. CRAWFORD, C. SHAGASS and T. J. PASHBY, Am. J. Ophth. **28**: 1220 (Nov.) 1945.

An abstract of the authors' summary and conclusions follow.

Data showing the quantitative relation between refractive error and visual acuity were presented for 325 eyes with simple myopia, 160 eyes with simple myopic astigmatism and 714 eyes with compound myopic astigmatism.

The results showed that visual acuity and refractive error are closely related, although factors other than refractive error influence measurements of visual acuity.

The data presented here permit for myopia the construction, in terms of refractive error, of visual standards which may be used to supplement the usual statement of such standards in terms of the Snellen test.

W. S. REESE.

Retina and Optic Nerve

THROMBOSIS OF CENTRAL RETINAL VEIN. H. J. STERN, Brit. J. Ophth. **28**: 643 (Dec.) 1944.

The case is reported to emphasize a warning regarding undue optimism in therapeutic attempts, especially in cases of younger persons, and to show that the complete spontaneous recovery from a serious condition is certainly possible and so-called cures should always be regarded with skepticism.

A physician aged 24 awoke with poor vision in the left eye. Ophthalmoscopic examination showed pronounced venous congestion of the retina with some hemorrhages. Vision was reduced to 2/60. The visual field was contracted concentrically. On his rising from the table after a roentgenographic examination, vision was found to be 6/12, the visual field nearly normal and the ophthalmic picture unchanged.

Several days later vision was again 2/60, and the fundus showed the fully developed picture of thrombosis of the central retinal vein. Vision slowly improved without treatment, so that after eight or ten weeks it was restored to normal and the visual field was only slightly constricted.

Three years have elapsed since this episode; the patient has remained in the best of health, and his eyesight has not changed. Photographs of the fundus showing the initial condition, the appearance when the thrombosis was at its height and the appearance after eight weeks are included.

W. ZENTMAYER.

ILLUMINATED ELECTRODE FOR RETINAL DETACHMENT OPERATION. T. COLLYER SUMMERS, Brit. M. J. **1**: 48 (Jan. 13) 1945.

The author believes that an incorrectly applied electric current explains macular degeneration and other field defects which occur after successful operations for detachment. He recommends that the hole be found by transillumination. A transilluminator designed by Gray Clegg, of Manchester, England, was modified so that the naked light was covered with ground glass. This reveals a hole in the macula clearly. Then it was decided to add an electrode around the light, as is well shown by the illustration which accompanies the article.

After the incision is made through the conjunctiva and Tenon's capsule on the outer side of the globe, the external rectus muscle is divided. The electrode transilluminator is then introduced, while the operator, with a nonilluminated ophthalmoscope, examines the fundus; when the light is opposite the hole, the current is turned on at 120 milliamperes for five seconds. Two applications are made, so that the hole is properly covered. Fluid is then let out with a diathermy needle of 2 mm. thickness and suction applied. It is important, before introducing the transilluminator, that the sclera be dry and free from blood.

ARNOLD KNAPP.

Therapeutics

CHOLINERGIC DRUGS AND KERATOPLASTY. F. VIDAL and J. MALBRÁN, Arch. de oftal. de Buenos Aires **19**: 409 (Oct.) 1944.

From their experience with keratoplasty, the authors conclude that the postoperative glaucomatous state which at times occurs in eyes on which keratoplasty has been carried out may take place without the presence of anterior synechia, which is considered the causative factor by most authorities. The authors believe that a disturbance in the nutrition of the cornea, thereby lessening its permeability, is at times the origin of the hypertension. This nutritional disturbance of the cornea is favorably influenced by the use of cholinergic drugs. The authors report 4 cases in which this treatment was used, in 3 of which good results were obtained.

H. F. CARRASQUILLO.

Society Transactions

EDITED BY DR. W. L. BENEDICT

COLLEGE OF PHYSICIANS OF PHILADELPHIA, SECTION ON OPHTHALMOLOGY

Burton Chance, M.D., *Chairman*

George F. J. Kelly, M.D., *Clerk*

April 18, 1946

Stevens-Johnson Disease: Report of a Case. DR. BRUCE A. GROVE and DR. EDMUND MEISENHELDER (by invitation).

Stevens-Johnson disease is generally considered a manifestation of erythema multiforme exudativum, first described as a clinical entity by von Hebra in 1866. The lesions occur in the conjunctiva as well as on the mucous membranes of the mouth, nose, pharynx, larynx, trachea, bronchus and genitalia. Conjunctivitis may be the first symptom of the general disease; and according to Duke-Elder it may take three forms, namely, a relatively mild catarrhal, a purulent and a severe pseudomembranous form.

The first recorded case of ocular involvement was described by Fuchs in 1876 as "herpes iris conjunctivae."

Staphylococcus aureus is more commonly found on culture than any other organism.

The disease is of sudden onset with high fever and pronounced constitutional symptoms, which gradually subside, and the patient usually recovers in eighteen to twenty-one days. Although prostration is severe, the mortality rate is low, only 4 deaths having been reported.

A review of the literature illustrates the confusion existing among authors as to the proper cataloging of the disease.

The case reported is that of a white man, aged 30, who first complained of light hurting his eyes. Examination revealed mild injection of the palpebral and bulbar conjunctiva. Within twenty-four hours he was violently ill, and his temperature rose to 103.2 F. There was a cutaneous rash, consisting of macules, papules and intracutaneous vesicles. Involvement of all the mucous membranes and mucocutaneous junctions and severe pseudomembranous conjunctivitis were noted.

The patient was discharged on the twenty-first day after onset with no loss of visual acuity, but with slight symblepharon, prominent scarring of the palpebral conjunctiva and occlusion of all the puncta.

Drug and serum reactions were ruled out as causative agents. Acute vitamin deficiency was suggested as an etiologic factor.

The authors concluded that Stevens-Johnson disease is a severe form of erythema multiforme exudativum with involvement of the conjunctiva, whether it be catarrhal, purulent or pseudomembranous.

Several slides were shown.

DISCUSSION

DR. JOHN F. WILSON: As the authors have stated, Stevens-Johnson disease is considered by many authorities to be erythema multiforme, and the slides well demonstrate the extensiveness of involvement which may occur in this disease. Not only were bullae present, but there were various other lesions on the skin, namely, macules, papules and pustules. Erythema multiforme produces multiform lesions, which may involve any of the dermal areas or the mucous membranes. The disease is thought to be due to a virus, although the virus has never been demonstrated. It is possible that in the authors' case a dietary deficiency lowered the patient's resistance so that such a virus gained a foothold.

It is important to differentiate the changes in the eyes in this case from those occurring with pemphigus vulgaris. Three outstanding characteristics, not directly related to the ocular structures, of this case will differentiate the disease from pemphigus vulgaris. First, as Dr. Grove mentioned, pemphigus usually occurs in older patients. This patient is now 30. He was about 28 at the time of the attack. Second, the onset of the disease, unlike that of pemphigus, was sudden and severe. Within twenty-four hours it had almost reached its peak, and from that time on the patient's condition gradually improved. Third, the entire course of the disease lasted nineteen days. Pemphigus, however, is characterized by a longer term, with exacerbations and remissions and ultimately a fatal outcome.

There is one type of pemphigus which could easily be confused with this condition, that is pemphigus of the mucous membranes, or localized pemphigus. This type is characterized by outbreaks of bullae in various areas, involving only small areas at a time. There are then relapses, with similar small areas becoming involved; but ultimately the reaction becomes generalized. The whole of the skin and mucous membranes is affected, and the disease terminates fatally. The course is chronic.

As Dr. Grove mentioned, Duke-Elder, in his conclusions, divides the ocular involvement of erythema multiforme into three types: the catarrhal, the purulent and the pseudomembranous. He believes, and most of us would agree with him, that these are differences of degree rather than of type. In other words, the pseudomembranous type shows the most severe changes involving the ocular structures. That point is aptly demonstrated by the penile lesion in this case. It bears a close relation to the ocular lesion and shows a similar bandlike scar, holding down the prepuce to the glans.

DR. W. ZENTMAYER: I shall not discuss the paper itself, but I want to comment on the title. This is not a criticism of the authors, for they have a precedent for their use of the name. It seems to me, however, that when a general disease has common ophthalmic complications, to make an entity out of cases in which those complications are a little more severe is of questionable validity. One might just as well speak of the Wheeler syndrome, for in Wheeler's case the disease was much more severe than usual, with development of panophthalmitis and loss of the eye. It seems to me that it is hard to justify the establishment of an entity for this group of cases of erythema multiforme

exudativum. Furthermore, there is an objection to the use of an author's name to designate a syndrome. It gives no indication of the nature of the disease, and when one is searching the literature for a certain condition one may overlook cases that are published under a syndrome bearing an author's name.

DR. BURTON CHANCE: I agree with Dr. Zentmayer, for it would be difficult to know to what condition the names of these two men refer. The title would have been understood if it had denoted a special type of erythema multiforme. I have seen this disease in a general way, but in no case was the eye involved as it was in the one which has been so interestingly presented.

Acquired Ophthalmic Allergy. MAJOR WILLIAM F. BONNER, Medical Corps, Army of the United States (by invitation).

1. Acquired allergy may be single or multiple.

2. The most common offender is atropine, which may cause dermatitis or intraocular hemorrhage.

3. Quinine amblyopia may be acquired, and in the case which was reported the condition was helped by administration of 50,000 units of vitamin A three times daily.

4. Hemorrhagic allergy was improved by use of Padutin (a pancreatic preparation).

Keratitis Associated with Lymphogranuloma Venereum. DR. HAROLD G. SCHEIE and (by invitation) DR. ALAN S. CRANDALL.

Four cases were discussed in which identical corneal lesions of a distinctive type were associated with lymphogranuloma venereum. Evidence supporting the designation of the virus of lymphogranuloma venereum as the etiologic agent was considerable.

1. The corneal lesion was so characteristic as to suggest the diagnosis of lymphogranuloma venereum in all the cases.

2. Diagnosis of the systemic disease was further established by additional clinical or laboratory evidence or both.

(*a*) In all cases the Frei test gave a positive reaction.

(*b*) In 2 cases scars of healed buboes and in 1 case active inguinal involvement were present.

(*c*) In the fourth case, there was no clinical evidence of lymphogranuloma venereum other than a strongly positive complement fixation reaction, and biopsy of the corneal lesion showed histologic changes compatible with the disease.

(3) The corneal lesion was always associated with a positive reaction to the Frei test and never with any disease other than lymphogranuloma venereum.

(4) The lesions were identical with those occurring in a case of lymphogranuloma venereum reported by Meyer and Reber in 1940.

DISCUSSION

DR. WERNER HENLE: My colleagues and I are glad to have had the opportunity to study in the laboratory 1 of the cases just presented. The

results we have obtained thus far serve well to demonstrate the possibilities, as well as the limitations, of laboratory studies in the diagnosis of virus infections.

There are three general approaches to the laboratory diagnosis of a virus disease: (*a*) isolation and identification of the causative agent; (*b*) determination of the serologic response of the patient and (*c*) demonstration of characteristic pathologic lesions. We have used all three avenues in this case, and in discussing it I shall begin with the third approach, the demonstration of characteristic lesions. Part of the material obtained for biopsy from the cornea was sectioned and stained with Giemsa's method (two slides). On examination many epithelial cells, and in some regions of the section practically all of them, contained cytoplasmic inclusions. These consisted of aggregations of small round bodies staining dark purple. In many places individual bodies or small groups of these particles were observed. They had a diameter of from 200 to 300 microns and represented probably the elementary bodies of the virus involved in this case. Such inclusions occurring with lymphogranuloma venereum were first fully described by Miyagawa as "granulocorpuscles."

The patient's serologic reactions were likewise in accord with what one would expect to find. The complement fixation test with Lygranum antigen (a brand of chick embryo antigen) gave a high serum antibody titer (1:256). The antigen used is the same material which is employed in the Frei test, which also gave a positive reaction, as the authors have pointed out.

Our studies on the isolation of the causative agent have not yet been completed. The number of elementary bodies visible in the section would imply that the virus should be isolated with ease. On the other hand, the high antibody level of the patient's serum may cause considerable difficulty. In order to release the virus from the cells, the tissue has to be emulsified by grinding in a mortar with an abrasive, and it is impossible to avoid the contact of antibody with the virus; thus, some virus may be neutralized before the injection of the emulsion into experimental animals.

The first attempt at isolation of the virus was made by intracerebral injection into white mice. No lesions developed and on the twelfth day the animals were killed and their emulsified brains passed to new mice. Again no lesions developed, and this line of investigation was discontinued.

A second attempt was made with the chick embryo. In this study, the remaining biopsy material, which had been kept at — 10 C., was injected into the yolk sac of 8 day old chick embryos. They survived eight days of further incubation, when the yolk sacs were harvested. A 20 per cent suspension was passed to new eggs, and also to white mice, by the intracerebral route. The mice showed some signs of cerebral lesions on the fourth and fifth days. They lost weight, and on suspension by the tail they exhibited tremor and had difficulty in regaining equilibrium on release. Passage of the emulsified brains of these mice to other mice produced severer lesions and death. At this point of the investigation we now stand. There is clearly a chance that the agent has been isolated from the biopsy material. If so, it has to be identified by neutralization of the agent with known specific

immune serums as well as with the patient's serum. The possibility of having activated a latent virus in the mice must be excluded.

What do the various data imply? The virus of lymphogranuloma venereum belongs to a group of agents which have been classified together on the basis of various properties they have in common. In this group of agents are found, besides the virus of lymphogranuloma venereum, the agents of psittacosis, ornithosis, meningopneumonitis, trachoma, inclusion blennorrhea, mouse pneumonitis and other virus diseases. They all form similar cytoplasmic inclusions and exhibit serologic cross reactions. Neutralization of the toxic activity of these agents, described by Rake and Jones, constitutes the most specific test and serves best to differentiate the various viruses of this group.

From the data presented, there is little doubt that the agent involved in the case presented belongs to this group of viruses, but we cannot yet say with definite assurance that it is a strain of the virus of lymphogranuloma venereum. Although all results seem to be in accord with this diagnosis, a differentiation of the various inclusions cannot be made with sufficient accuracy. The high complement fixation titer with Lygranum antigen appears significant but may not be out of the range of cross reactions observed with some of the other viruses of this group. Fairly strong cross reactions with Lygranum antigen have been reported, for instance, with serum from patients with psittacosis and pneumonitis. The Frei test, too, has been found to give a weakly positive reaction in some cases of psittacosis, meningopneumonitis and atypical pneumonia. The final diagnosis hinges on the isolation and characterization of the causative agent. This has not been accomplished as yet, but, as I pointed out, there is a good chance that we may be successful.

DR. I. S. TASSMAN: I should like to ask the authors whether they observed the characteristic conjunctival lesion also in any of these cases of lymphogranuloma venereum. I believe that the typical lesion of this disease occurs on the conjunctiva and that it is unusual for keratitis to occur as a manifestation of this condition. Can they state just what it is in this form of keratitis which is typical or characteristic of lymphogranuloma venereum?

I have recently observed 2 cases similar to the ones described in which the condition cleared up under treatment with sulfonamide drugs and a third case in which improvement followed penicillin therapy. There was no clinical evidence of lymphogranuloma venereum in any of these cases, although laboratory tests were not made.

As Dr. Henle pointed out, there are several other conditions in which the Frei test may give a positive reaction. It does seem that the authors' case in which the laboratory findings were positive can be accepted as a real case of lymphogranuloma venereum. In the others, however, the diagnosis would be presumptive.

DR. WARREN S. REESE: I should like to ask whether this lesion bears any resemblance to the so-called salmon patch seen in interstitial keratitis.

DR. GEORGE F. J. KELLY: Does sulfonamide therapy alter the results of subsequent Frei tests? The recurrences reported in 2 cases were thought to be due to inadequate treatment. Is there any known standard of treatment for prevention of recurrences?

DR. ALAN S. CRANDALL: It might be interesting to show how the presumptive diagnosis was made in the last case. The patient had been seen several times, and lymphogranuloma venereum was not suspected until we examined a photograph which Dr. Scheie brought back from India, showing keratitis in a patient with a condition so diagnosed. The similarity of the lesions was so striking that we immediately started to study our patient with this disease in mind.

From the evidence in these few cases, I believe that the lesion is characteristic of lymphogranuloma venereum. However, by the time the lesion becomes typical there is permanent corneal damage. There will be some scarring and vascularization, and it would be well if the index of suspicion were high enough to prompt adequate treatment before the permanent damage occurs. I should like to reiterate the importance of continuous treatment for at least three weeks. The 2 patients who did not do well did not keep up adequate therapy.

DR. HAROLD G. SCHEIE: First, I believe there is little question that the lesion discussed is primarily keratitis rather than conjunctivitis. In the 1 patient who was seen early, the onset was associated with symptoms of conjunctivitis, but the corneal lesion promptly appeared. In all the cases we have discussed, as well as in the case reported by Meyer and Reber, the conjunctiva seemed to show only secondary injection. There were no granulating lesions on the conjunctiva, and adenopathy was not observed.

The appearance of the corneal lesion seems characteristic of and specific for the disease. Most important is examination with the slit lamp. The cornea is involved through its entire depth. The lesion first appears within the upper portion of the limbus. In 2 of these cases a similar corneal infiltrate subsequently developed within the lower portion, which also became vascularized. The vascularization is quite characteristic. The vessels are all superficial and resemble an epaulet extending onto the cornea from the upper part of the limbus, elevating its surface. The vascularized area does not stain. The lower border of the vascularized area is sharply delimited, no isolated vessels growing into the infiltrate in front of the vascularized zone.

The patient first seen in the clinic of the Hospital of the University of Pennsylvania by Dr. Crandall was presented and discussed at one of the weekly conferences of the clinic. The final conclusion reached by the staff members was that neoplasm had definitely to be excluded as a diagnostic possibility because of the new vessels and the elevation of the surface of the cornea.

Dr. Reese asked what resemblance these vessels had to the "salmon patch" of interstitial keratitis. The vessels in keratitis associated with lymphogranuloma venereum are superficial rather than deep, as in interstitial keratitis.

Dr. Kelly asked about the effect of sulfonamide compounds on the Frei test. It has none, and the reaction to the Frei test remains positive for life. This explains why the Frei test can be confusing and the diagnosis of lymphogranuloma venereum as the cause of any lesion must remain presumptive until the virus can be recovered.

Our last case was the most conclusive one we have had to present. The patient gave a positive reaction to the Frei test and a very strongly positive complement fixation reaction as well. Biopsy of the corneal

lesion showed changes compatible with the diagnosis of lymphogranuloma venereum, and now the virus inoculations seem to be giving positive results.

Finally, I might say that none of my colleagues or I have seen this corneal lesion in any patient who did not show at least a positive reaction to the Frei test for lymphogranuloma venereum. Even so, the diagnosis is still presumptive.

Pigmented Nevus of the Iris Treated by Iridectomy. DR. JAMES S. SHIPMAN and DR. P. ROBB MCDONALD.

A white woman aged 59 had had a spot on the iris of the left eye as long as she could remember. Recently it had increased slightly in size. A tumor was noted in the lower temporal quadrant of the left iris. The growth extended from about 1 mm. from the pupillary margin to the iridocorneal angle. The ciliary body was not involved. The tumor was removed by iridectomy, both operation and convalescence being uneventful. A diagnosis of leiomyoma was made by Dr. Perce DeLong and of nevus by Dr. A. B. Reese. Dr. Reese stated the lesion was a true nevus of the iris, since nevus cells were present.

The tumor was completely removed at operation, and when the patient was last seen vision in the left eye was correctable to 6/6.

DISCUSSION

DR. PERCE DELONG: The tumor under question has been submitted to many pathologists, and varied diagnoses have been obtained. Some expressed the belief that it was malignant; others, that it was a nevus in an unusual location in the iris, and others, that it was a myoma.

Nevi of the iris usually grow from the anterior surface. This neoplasm arose from the substructure. It is unusual for a nevus to develop from this location.

The microscopic picture showed no special arrangement; i. e., there was no alveolar arrangement of cells, commonly spoken of as nevoid bodies, nor did the tumor contain epithelioid cells—both common in nevi. Instead, the cells were arranged in whorls. They were long spindle cells and possessed many fibrils. Also, with the phosphotungstic acid hematoxylin stain the nuclei showed an acidophilic reaction, a characteristic common to myoma; for this reason, I feel that this tumor is a neoplasm.

DR. W. ZENTMAYER: In 1 of 2 cases occurring in my experience the same difference of opinion existed among the pathologists. The boy had a fleshy growth of the iris, which I removed according to the technic described tonight.

The diagnosis of the first pathologist who examined the growth was leukosarcoma. He submitted it to a second pathologist, who made a diagnosis of leiomyoma. Because of this difference of opinion, it was examined by a third pathologist, who confirmed the diagnosis of the first pathologist. It was later studied by Colonel James E. Ash, who agreed with the second pathologist that it was a leiomyoma.

DR. W. E. FRY: I had the opportunity of seeing Dr. Zentmayer's patient at the time of operation, as well as of studying the slide after the section was prepared. The case was somewhat similar to one which I previously studied, as did Dr. Adler and Dr. Waite, the difference

being chiefly that in the latter a contact glass was useful in determining the presence of a free angle.

I saw the slides in Dr. Shipman's case and have talked to both Dr. DeLong and Dr. Reese, and I think there are reasons for the differences in opinion. There could be some controversy in regard to the cells. I believe that this was a tumor in which the pigment-bearing cells were important, a malignant melanoma. Certainly, the patient was properly treated.

Dr. Burton Chance: Dr. Zentmayer's case had certain aspects rather like those of a case of my own. The tumor was removed in a manner similar to that described by Dr. McDonald. The patient had had all sorts of diagnoses. There had been a gradual yet appreciable growth in the previous five years. The tumor proved to be a mixed cell sarcoma. I was under stress by the patient's insistence that I should remove the eye immediately if the mass were malignant. The onus of the decision was assumed by the patient. With the assent of Drs. Posey and Madison Taylor, an otherwise perfectly healthy eye was excised. That was twenty-odd years ago. Recently I learned that the patient had been in perfect health ever since the operations.

Dr. Edmund B. Spaeth: I have never seen a more beautiful photograph of an eye than the one Dr. McDonald showed. The photographs presented by Drs. Grove and Scheie were also excellent. Presentations like these illustrate the value of good photography in recording pathologic conditions.

Dr. James S. Shipman: No less an authority than Duke-Elder states that present ideas as to the nature and classification of neuroectodermal tumors are in a state of flux. It was not until 1910 that Verocay showed that these tumors were derived from a proliferation of the cells of the sheath of Schwann, and therefore of ectodermal origin.

Masson, from 1926 to 1932, confirmed this opinion and revolutionized all previous conceptions of neuroneoplasms. His researches were also confirmed by Stewart and Copeland, in 1931; by Foot, in 1932, and by others. Masson showed that cutaneous nevi arose from a neoplastic proliferation of the specialized end organs of the cutaneous nerves, namely, the Meissner corpuscle, in the dermis, and the Merkel-Ranvier corpuscle and chromatophore, special types of cells in the basal layers of the epithelium.

As a result of these observations, according to Duke-Elder, it appears that a number of tumors which used to be described in the literature as neurofibroma, plexiform neuroma, ganglionic neuroma, nevus, melanoma and certain types of sarcoma are neurogenic, the fundamental cell of origin being the cell of Schwann.

According to Duke-Elder and Algernon Reese, nevi usually occur in the skin or conjunctiva or at the junction of these two structures, and they are neuroepithelial in origin, springing from the end apparatus of the sensory nerves, which may be pigmented or nonpigmented.

The term melanoma seems to have been rather loosely used to describe a pigmented tumor in any part of the body and has no real value in indicating the origin or the malignancy of the tumor. As has been pointed out in the presentation of this case, a pigmented tumor may be congenitally present in the iris for many years with no evidence

of growth or increase in size until suddenly, for some unknown reason, it takes on the characteristics of a malignant growth, as shown by its increase in size and extension into the angle of the anterior chamber, with resulting increase in the intraocular tension.

Certainly, these signs should always make one suspicious of its malignant character and advise operation, as was done in this case, with the hope of removing the tumor in its entirety before it has invaded too far the angle of the anterior chamber.

I feel that this case demonstrates the necessity of careful observation. Dr. Roth, who saw this patient and referred her to me, is to be congratulated on his acumen in judging the time for surgical intervention. I am indebted to him for having referred this patient to me. I am more indebted to Dr. Zentmayer, who confirmed our opinion as to the operation to be performed and who, more than that, taught me just how it should be done. I had the pleasure of being his assistant at a similar operation for just such a tumor of the iris about nineteen years ago, when I was a resident at the Wills Hospital.

This case has been presented as a preliminary report, with the hope of stimulating discussion and interest in tumors of the iris. Dr. McDonald and I hope to give a more complete report of this case at a later date, when a more definite diagnosis has been agreed on.

NEW YORK ACADEMY OF MEDICINE, SECTION OF OPHTHALMOLOGY

Brittain F. Payne, M.D., *Chairman*

Milton Berliner, M.D., *Secretary*

May 20, 1946

INSTRUCTION HOUR

Roentgenography in Ophthalmic Diagnosis. DR. RAYMOND L. PFEIFFER.

After listing and evaluating various indications for the use of roentgen rays in ophthalmology, the author selected several conditions which afforded an opportunity for the demonstration and discussion of recent contributions of roentgenology to the study of diseases of the eye. The value of the roentgenogram in the diagnosis of retinoblastoma was considered. Deposits of calcium were found in approximately 80 per cent of a large series of cases, and calcium was observed microscopically in only an additional small per cent. Internal fracture of the orbit was demonstrated as the cause of enophthalmos in cases in which there was no external bony deformity. Intracerebral deposits of calcium as the most important diagnostic finding in toxoplasmosis were shown in a series of 9 cases, in most of which the author made clinical as well as roentgenographic examinations. The value of roentgenography in the study of exophthalmos was emphasized by his figures in a series of 200 consecutive cases, in 70 per cent of which changes were demonstrated roentgenologically. In 42 per cent of all cases the changes were diagnostic. The character of these diagnostic findings was then illustrated by the presentation of a number of cases of each.

REPORT OF CASES

Anomalies of the Iris: Report of Two Cases. DR. J. J. SAUER.

CASE 1.—*Congenital malformation of the iris.*

W. B., aged 60, was seen on June 12, 1943, for a change of glasses. A "colored spot" had been noticed in his right eye by a member of his family about twenty years before; as far as he knew, it had not increased in size.

On examination, the right eye presented an ovoid, fairly regularly outlined, chocolate brown pigmented area on the posterior surface of the cornea from about 12:30 to 5 o'clock, extending from the limbus toward the pupillary area about 4 mm. Just inside the limbus, and measuring 0.5 mm., was a crescentic clear band, through which the normal structure of the iris could be seen. A sharply demarcated, ovoid, lighter brown area lay in the underlying iris from 2 to 4 o'clock; this did not extend to the pupillary edge of the iris, and the adjacent pupillary border was straightened vertically. No vessels were visible. The anterior chamber was of normal depth, and the two pigmented surfaces were not joined. On transillumination there was no suggestion of a tumor. Ophthalmoscopic examinaton failed to reveal any bulging posteriorly or other change. The left eye was normal. The last examination, on May 9, 1946, showed no change in the condition.

Melanosarcoma and cyst were ruled out, and the diagnosis of congenital malformation was made. The probable pathogenesis was as follows: Atrophy of the anterior layer of the iris led to the formation of a defect, or gap, through which the pigmented layer of the iris protruded and became adherent to the posterior surface of the cornea, giving rise to the pigmented area on the cornea. This adhesion later separated from the cornea, leaving pigment on the posterior surface of the cornea.

CASE 2.—*Bilateral cyst of the pigment layer of the iris.*

C. D., aged 45, was examined on Jan. 4, 1944, for a change of glasses. In the right eye a smooth, globular brownish cystic mass was just barely visible within the temporal pupillary area from 8 to 11 o'clock; it lay behind the iris and protruded into the area anterior to the lens. The left eye presented a similar but larger mass which was also visible in the temporal pupillary area from 1 to 6 o'clock; it arose from behind the iris and protruded into the pupillary area, anterior to the lens. When the pupils were dilated, these cystic masses were more clearly visible and extended farther into the pupillary areas. On transillumination there was no interference with the passage of light. Ophthalmoscopic examination revealed nothing abnormal.

The diagnosis of bilateral cyst of the iris was made from the symmetric location, the smooth surface, the lack of vascularity, the globular shape and the absence of interference with the passage of light.

DISCUSSION

DR. ARNOLD KNAPP: I was particularly interested in a feature of Dr. Sauer's first case which concerns the bulging, pigmented area in a defect of the mesodermal layer of the iris. When the pupil was dilated, the iris partly covered the pigmented area and flattened it out, an

observation which did not suggest either a tumor or a cyst. In my opinion, this case belongs with malformations of the iris. Within the last few weeks the patient was seen at the Institute of Ophthalmology for a check with the drawing made in 1943; and then Dr. DeVoe was able to make a gonioscopic examination, which I think will add a great deal of information to the interpretation of the case.

DR. GERARD DEVOE: The gonioscopic examination showed clearly that the lesion was not a cyst. The pigment on the cornea seemed to have been deposited there, having perhaps been shaken off from the pigment epithelium of the iris. The anterior layer of the iris was missing; and all that was left was the pigment epithelium, which was very thin and freely movable. It was interesting to note the difference between the appearance three years ago and that of a few days ago, in that now the pigment epithelium had become attached to the corneoscleral area.

DR. RUDOLF AEBLI: Would Dr. Knapp enlighten us on how to account for the pigment on the posterior surface of the cornea?

DR. ARNOLD KNAPP: When I saw the patient, the pigment layer of the iris was bulging and in contact with the posterior surface of the cornea; I though, therefore, that the pigment must have been deposited, just as Dr. DeVoe says, and when the iris flattened down a deposit remained on the posterior surface of the cornea.

DR. RUDOLF AEBLI: If these two structures were in contact, what subsequently separated them?

DR. ARNOLD KNAPP: The separation was probably caused by the reformation of the aqueous. The adhesion could not have been very strong.

PAPERS OF EVENING

Extraction of Cataract in the Presence of Fluid Vitreous. DR. DANIEL B. KIRBY.

The author gave his concept of the cause of the development of cataract and of the change from normal gel, or viscid vitreous, to vitreous in the fluid state. He stressed the preliminary examination of the patient's eyes, in particular by means of ophthalmoscopy, slit lamp microscopy and tonometry, and the necessity of being on the alert for signs of degeneration or inflammation. In some cases it is possible to recognize the condition and to be aware of the presence of fluid vitreous before operation is begun. In certain instances, however, in which the fluid vitreous is in communication with the anterior chamber, the surgeon may not be aware of the condition until he has made his section and then has observed the fluid vitreous seep away. Sutures placed after the section are satisfactory in such cases, whereas it is important to place sutures before section if there is any likelihood that viscid vitreous will be lost. When the sutures are placed after section, the cataract is delivered by traction, rotation and stripping of the zonule, if the latter is resistant. The loop may be used to support the lens and bring it forward but should not be the only means of traction, as the zonule is not ruptured easily enough by traction alone. Pressure on the outside of the globe is contraindicated, because it is ineffective and adds to the complication. Such eyes react better to intracapsular

extraction than to capsulotomy and expression. Two short series of cases of cataract were reported in which the results in eyes in which the fluid vitreous was well contained behind the capsulozonular-hyaloid barriers were compared with results in eyes in which the fluid vitreous was in communication with the anterior chamber. Satisfactory results were obtained with observance of the surgical principles outlined.

DISCUSSION

Dr. Watson Gailey, Bloomington, Ill.: I am sorry that Dr. Kirby did not discuss the conservation of viscid vitreous during the course of cataract extraction. I am always apprehensive about the spilling of vitreous, whether viscid or fluid, but I think I manage my cases with fluid vitreous much better than I do those with viscid vitreous. The "fish mouth" wound which follows immediately after delivery by the intracapsular method is very annoying and distressing.

Dr. Arnold Knapp: I should like to emphasize two points in Dr. Kirby's interesting paper. First, in my judgment, it is a mistake not to put in preliminary sutures before operating if there is any opportunity for loss of vitreous. Second, if fluid vitreous is encountered, an iridectomy should always be done. In the presence of prolapse of the vitreous the question arises: How fluid is the vitreous, and how great is the subluxation of the lens? I should like to remind the members of the Section of a method suggested by Dr. Herman Knapp many years ago by which he was able to extract the dislocated lens by manipulation with external pressure. This method may be considered when the vitreous is thick. In recent years the late Dr. Jameson published a similar procedure. In cases in which there is a fairly normal vitreous the lens will frequently return into position after a few days and thus facilitate the extraction. To fish for a completely dislocated lens in fluid vitreous is very hazardous. Van der Hoeve suggested a procedure through which by placing a suture under the insertion of each of the rectus muscles and by pulling on the sutures the eye was drawn forward and no pressure could be exerted on the sclera.

Dr. John McLean: Dr. Kirby's paper does not leave much room for discussion, but there are a few points on which I should like to hear him comment further. One is the argument over retrobulbar injection. Inasmuch as retrobulbar injection tends to soften the globe and it is a simple principle of hydrodynamics that fluids do not flow uphill, so that vitreous to flow out of the eye must be pushed out either by the patient or by the surgeon, is it not worth while, particularly with fluid vitreous, to use retrobulbar injection as a routine, in order to make it harder for the patient and the surgeon to push the vitreous out?

I do not quite follow Dr. Kirby's reasoning about not using preplaced corneoscleral sutures when fluid vitreous is present or is suspected. Not long ago I watched with some horror one of the strong advocates of placing sutures after section practically wallowing in vitreous, which had escaped immediately after the section, while he wasted time and vitreous in getting down to the fundamental business of dealing with the lens and the vitreous; and I felt he would have saved time, effort and vitreous if his sutures had been there before the eye was opened.

The third point on which I should like to hear Dr. Kirby comment is his choice of delivery of the lens in a case of fluid vitreous by grasping it above, when it would seem that a somewhat better barrier to premature loss of vitreous would be provided by dislocating the lens below first, grasping it below and tumbling it, so that the zonule is left as intact as possible above.

DR. PURMAN DORMAN, Seattle: Some of my fellow ophthalmologists and I have become accustomed to making a keratome incision for cataract extraction. If fluid vitreous is anticipated, a preliminary canthotomy is done. We have always admired the smoothness of the linear knife incision as done by Dr. Kirby. Skill even approaching his is not always maintained. The keratome incision may be better placed by those of us who are less deft. Perhaps Dr. Kirby will comment on this habit of ours of using the keratome incision and the preliminary canthotomy.

DR. RUDOLF AEBLI: My own experience is that when the vitreous has been lost my preparation has been inadequate. I have come to the conclusion that a perfect akinesia, with an external canthotomy and injection of the muscle cone, is the best guaranty against loss of vitreous.

DR. DANIEL B. KIRBY: I appreciate the discussion. There is great interest in any phase of cataract surgery, particularly in the problem of loss of vitreous.

Dr. Gailey, the matter of viscid vitreous opens up a whole new chapter. I should like to study the problem for a year or two before I talk about it further.

I appreciate Dr. Knapp's discussion. He has had great experience and is very wise in his surgical treatment. I should always do an iridectomy if there was viscid or semifluid vitreous in the wound, but I have seen cases in which the results were very good with what is called completely fluid vitreous. I have not had experience with Verhoeff's technic, but it sounds logical.

Dr. McLean, I do not believe that retrobulbar injection always softens the eye. I have given up retrobulbar injection except with the younger patients, who have good vessels. I have seen cases in which extravasation of fluid and blood into the orbit pushed the eye forward.

Dr. Dorman mentioned external canthotomy. I used to do many canthotomies before I gave up retrobulbar injections.

Dr. McLean says that vitreous will not flow out but has to be pushed out. I do not believe that is true in regard to fluid vitreous, for there is the weight of the sclera and of the surrounding tissues and the effect of their collapse on the fluid vitreous; I am sure that in the cases I reported I was not pushing the fluid vitreous out.

The question of preplaced sutures requires separate discussion. I am in accord with Dr. McLean on the value of sutures in cases of viscid vitreous, but I should not place them in every ordinary case. The mode of inserting them by the average surgeon often results in more trauma than it should. They are often in the way. There are many advantages in grasping the capsule above. I do not like to grasp it below, particularly in a case of fluid vitreous in which the lens drops back to the posterior position. One cannot see what one is doing unless the corneal flap is raised. I have never seen any bad results from raising the corneal flap. I believe it is a most conservative procedure. I do the iridectomy

and place the lens capsule forceps under direct view. If the surgeon must place a foreceps below when the lens is far posterior and must reach well in to pick it up, there is not the chance of completing the operation as satisfactorily as when the capsule is grasped above.

I do not see any reason for the recent trend to use of the keratome. Unless there is some complication, the Graefe knife is very satisfactory, and there is no reason for not adhering to its use. It gives a cleaner section and less trauma at the beginning of the operation. It is necessary to make less section with the scissors. In a letter which I received from Traquair the other day, he said that he relied on anesthesia, complete local anesthesia, rather than on akinesia. I think that both are important, Dr. Aebli, and that you are right about careful preoperative preparation in avoiding complications. I do not pretend to know much about the matter of viscid vitreous.

Onchocerciasis in Guatemala: A Preliminary Report. Dr. William B. Clark, New Orleans.

I was invited to participate in a study of onchocerciasis in Guatemala in 1945 by the Pan-American Sanitary Bureau. The investigation was carried out in Yepocapa, a village of 8,000 inhabitants in the Department of Chimaltenango. A study of the insect carriers and the habits of the Onchocera volvulus revealed that man is the true host and that the parasites are picked up by a fly of the genus Simulium when it bites. After maturity, the parasites enter the proboscis of the fly, where they are ready to reenter the host when the fly pierces the skin. The larvae then migrate through the subcutaneous tissue until they find a suitable place to make a nodule. It is from the nodules that adult worms can be taken. All stages of development may be seen, from the egg to the microfilarias breaking out of the shell. The average size of the microfilarias is about 8 by 300 microns; so the larva must be magnified about twenty-two times for it to be seen in the anterior chamber and for the details of its movements to be visible.

My colleagues and I reexamined 1,215 patients known to have, or suspected of having, onchocerciasis. A complete ophthalmic examination was made of each patient. In addition, biopsies of the skin and conjunctiva were done. In all cases in which biopsy showed positive changes in the conjunctiva or an aqueous flare was seen, we did a paracentesis and examined the aqueous under the microscope.

Of 62 of these patients, the aqueous of 29 showed the presence of two or more microfilarias. We also did a paracentesis on several patients who complained of entoptic vision but who had no positive changes in the conjunctiva, and in no case did we find microfilarias in the aqueous. Another remarkable observation was that none of the 29 patients from whom we recovered the microfilarias from the anterior chamber complained of entoptic vision. To me, the most striking features were the anterior chamber literally filled with microfilarias without injection of the eye and the changes produced in the cornea and iris by this infection without ciliary injection.

Of the 1,215 patients examined, 967 had nodules or had previously had nodules removed. The prevalence of nodules; the results of biopsy of the skin and conjunctiva and of paracentesis, and the lesions of the cornea, iris and fundus are tabulated.

Only one eye was obtained for pathologic study, which has not been completed. The eye was removed because of the pain associated with an attack of secondary glaucoma.

DISCUSION

DR. BERNARD FREAD: What measures are taken by travelers to Guatemala to avoid getting this disease?

DR. ALGERNON REESE: What is the treatment for the disease?

DR. WILLIAM B. CLARK, New Orleans: I do not think that an occasional bite from the simulium is dangerous. I had several bites on my bald head while making this study and the members of my brigade were also bitten, and in none of us did nodules develop. The ordinary insect repellent used by the armed forces keeps the flies away. We used this in the beginning; but, as always, we became careless toward the end and left it off until we got a bite. The bite is quite painful and stings for a few minutes, and it usually leaves a red wheal, which may persist for several hours. Many of the managers of the coffee *fincas* are of Swiss or German extraction, and some of them have lived in the zone as long as forty years without becoming infected. However, occasionally some one other than an Indian will appear with the infection.

Removal of the tumors after they occur is the accepted form of treatment, but in my opinion this is of questionable value. Part of our project was to try certain new drugs sent down by the Institute of Health, but the physician who was to administer them was transferred and the situation caused by his leaving was not cleared up by the time we had completed our ophthalmic survey. I hope that before we make a final report on this subject we shall have information on the response of the microfilarias to drug therapy.

Book Reviews

Archivos de la Asociación para evitar la Ceguera en Mexico. (Archives of the Association of Prevention of Blindness in México). Vol. III, Pp. 282. México, 1945. Director, Dr. L. Sanchez Bulnes; Editor, Dr. Daniel Silva. Gomez Farias Num 19, México, D.F.

The book begins with a report of the work done in the hospital of this association in México, D. F., during 1944 and a description of the activities in the various departments. Then follow a number of articles; the longest and most important is the one on "Ocular Onchocerciasis in Chiapas" by Amselmo Fonte Bárcena. The author gives a history of the ocular complications of onchocerciasis reported since 1916, when Robles described them for the first time. The ocular symptoms are dominated by photophobia and blepharospasm, which in some cases are so severe that the patient cannot open his eyes at all. Besides photophobia, the patient complains of burning and a sensation of a foreign body in the eyes. These symptoms occur in attacks and disappear gradually when the infected nodules are removed.

The ocular findings vary with the acute and chronic stages of the disease. In the acute form there is pronounced, red edema of the face, more conspicuous in the lids and cheeks, which Robles termed "erysipela of the coast." The eye itself shows ciliary and conjunctival congestion, chemosis and increased fine, superficial vascularization of the tarsal and bulbar conjunctiva.

In the chronic forms the ocular signs are reduced mainly to vascularization, pigmentation and edema of the conjunctiva. The vascularization takes place in the conjunctival and ciliary vessels, nasal and temporal to the cornea in a triangular area; it fades gradually toward the periphery. The pigmentation is brown in color, pericorneal, located nasally and temporally and appears as a fine dusting of the conjunctival epithelium.

The severity of the ocular symptoms mentioned here has no relation to the local changes. Bárcena expressed the belief that they are due to a toxic substance produced by the adult parasite at the time of birth of the microfilarias and, to a lesser degree, to the presence of the latter. He advanced the hypothesis that the substance produced by the parasite is a derivative of the porphyrin.

The other articles treat of motility of the intraocular cysticercus, blindness caused by quinine, injections of hypertonic solution of sodium chloride in treatment of detachment of the retina, importance of ophthalmic examinations in cases of cranial injuries, use of anesthesia in the cataract operation, contact lenses, tuberculosis of the choroid, clinical applications of angioscotometry, vegetative innervation of the visual apparatus and new instruments for dacryocystorhinostomy. Then there are four articles by authors from the United States. Obituaries of Dr. Rafael Silva and of Dr. Sanford R. Gifford conclude the volume.

H. Escapini.

Directory of Ophthalmologic Societies *

INTERNATIONAL

International Association for Prevention of Blindness

President: Dr. P. Bailliart, 66 Boulevard Saint-Michel, Paris, 6e, France.
Secretary-General: Prof. M. Van Duyse, Université de Gand, Gand, Prov. Ostflandern, Belgium.
All correspondence should be addressed to the Secretariat, 66 Boulevard Saint-Michel, Paris, 6e, France.

International Ophthalmologic Congress

President: Prof. Nordenson, Serafimerlasarettet, Stockholm, Sweden.
Secretary: Dr. Ehlers, Jerbanenegade 41, Copenhagen, Denmark.

International Organization Against Trachoma

President: Dr. A. F. MacCallan, 17 Horseferry Rd., London, England.

Pan-American Congress of Ophthalmology

President: Dr. Harry S. Gradle, 58 E. Washington St., Chicago.
Executive Secretaries: Dr. Conrad Berens, 35 E. 70th St., New York. Dr. M. E. Alvaro, 1511 Rua Consolacão, São Paulo, Brazil.
Place: Habana, Cuba. Time: February 1948.

FOREIGN

All-India Ophthalmological Society

President: Dr. B. K. Narayan Rao, Minto Ophthalmic Hospital, Bangalore.
Secretary: Dr. G. Zachariah, Flitcham, Marshall's Rd., Madras.

British Medical Association, Section on Ophthalmology

President: Dr. W. Clark Souter, 9 Albyn Pl., Aberdeen, Scotland.
Secretary: Dr. Frederick Ridley, 12 Wimpole St., London, W. 1.

Chengtu Ophthalmological Society

President: Dr. Eugene Chan.
Secretary: Dr. D. S. Shen, Eye, Ear, Nose and Throat Hospital, Chengtu, Szechuan, China.
Place: Eye, Ear, Nose and Throat Hospital, Chengtu, Szechuan, China.

Chinese Ophthalmology Society

President: Dr. C. H. Chou, 363 Avenue Haig, Shanghai.
Secretary: Dr. F. S. Tsang, 221 Foochow Rd., Shanghai.

Chinese Ophthalmological Society of Peiping

President: Dr. H. T. Pi, Peiping Union Medical College, Peiping.
Secretary: Dr. C. K. Lin, 180 Hsi-Lo-yen Chienmeng, Peiping.
Place: Peiping Union Medical College, Peiping. Time: Last Friday of each month.

* Secretaries of societies are requested to furnish the information necessary to make this list complete and keep it up to date.

FACULTY OF OPHTHALMOLOGISTS

President: Brig. Sir Stewart Duke-Elder, 63 Harley St., London, W. 1, England.
Secretary: Mr. Frank W. Law, 45 Lincoln's Inn Fields, London, W. C. 2, England.

GERMAN OPHTHALMOLOGICAL SOCIETY

President: Prof. W. Lohlein, Berlin.
Secretary: Prof. E. Engelking, Heidelberg.

HUNGARIAN OPHTHALMOLOGICAL SOCIETY

President: Prof. I. Imre, Budapest.
Assistant Secretary: Dr. Stephen de Grósz, University Eye Hospital, Máriautca 39, Budapest.
All correspondence should be addressed to the Assistant Secretary.

MIDLAND OPHTHALMOLOGICAL SOCIETY

President: Dr. W. Niccol, 4 College Green, Gloucester, England.
Secretary: Mr. T. Harrison Butler, 61 Newhall St., Birmingham 3, England.
Place: Birmingham and Midland Eye Hospital.

NORTH OF ENGLAND OPHTHALMOLOGICAL SOCIETY

President: Mr. E. F. Wilson, 24 Upper Northgate St., Chester.
Secretary: Mr. William M. Muirhead, 70 Upper Hanover St., Sheffield 3.
Place: Manchester, Leeds, Newcastle-upon-Tyne, Liverpool, Sheffield and Bradford, in rotation. Time: October to May.

OPHTHALMOLOGICAL SOCIETY OF AUSTRALIA

President: Dr. J. Ringland Anderson, Astor House, 108 Collins St., Melbourne, Victoria.
Secretary: Dr. D. A. Williams, 27 Commonwealth St., Sydney.
Place: Melbourne. Time: Oct. 20-26, 1946.

OPHTHALMOLOGICAL SOCIETY OF EGYPT

President: Prof. Dr. Mohammed Mahfouz Bey, Government Hospital, Alexandria.
Secretary: Dr. Mohammed Khalil, 4 Baehler St., Cairo.
All correspondence should be addressed to the secretary, Dr. Mohammed Khalil.

OPHTHALMOLOGICAL SOCIETY OF HOSPITAL DE NUESTRA SEÑORA DE LA LUZ

Chairman: Dr. Manuel J. Icaza y Dublán, México, D. F., Mexico.
Secretary: Dr. Jorge Meyrán, México, D. F., Mexico.

OPHTHALMOLOGICAL SOCIETY OF SOUTH AFRICA

President: Dr. A. W. Sichel, National Mutual Bldg., Church Square, Cape Town.
Secretary: Dr. J. K. de Kock, Groote Kerk Bldg., 32 Parliament St., Cape Town.

OPHTHALMOLOGICAL SOCIETY OF THE UNITED KINGDOM

President: Mr. Charles B. Goulden, 89 Harley St., London.
Secretary: Mr. Frank W. Law, 30 Devonshire Pl., London, W. 1.
Place: London. Time: May 30-June 1-2, 1946.

OPHTHALMOLOGY SOCIETY OF BOMBAY

President: Dr. D. D. Sathaye, 127 Girgaum Rd., Bombay 4, India.
Secretary: Dr. H. D. Dastur, Dadar, Bombay 14, India.
Place: H. B. A. Free Ophthalmic Hospital, Parel, Bombay 12. Time: First Friday of every month.

Oxford Ophthalmological Congress

Master: Mr. P. G. Doyne, 60 Queen Anne St., London, W. 1, England.
Secretary-Treasurer: Dr. F. A. Anderson, 12 St. John's Hill, Shrewsbury, England.
Time: July 4-6, 1946.

Palestine Ophthalmological Society

President: Dr. Arieh Feigenbaum, Abyssinian St. 15, Jerusalem.
Secretary: Dr. E. Sinai, Tel Aviv.

Philippine Ophthalmological and Otolaryngological Society

President: Dr. Antonio S. Fernando, Philippine General Hospital, Manila.
Secretary-Treasurer: Dr. José N. Cruz, Philippine General Hospital, Manila.

Polish Ophthalmological Society

President: Dr. W. Kapuściński, 2 Waly Batorego, Poznań.
Secretary: Dr. J. Sobański, Lindley'a 4, Warsaw.
Place: Lindley'a 4, Warsaw.

Puerto Rico Medical Association, Section of Ophthalmology and Otolaryngology

President: Dr. José T. Picó, Avenida Ponce de Leon 15, San Juan 10.
Secretary: Dr. Ricardo F. Fernández, Avenida Ponce de Leon 15, San Juan 10.

Revista Brasileira de Oftalmologia

President: Dr. Caldas Britto, Largo de Carioca 5-6° andar, Rio de Janeiro, Brazil.
Secretary: Dr. Evaldo Campos, R. Rodrigo Silva 7-1° andar, Rio de Janeiro, Brazil.
Place: Rio de Janeiro, Brazil. Time: Third Friday of every month from April to December.

Royal Society of Medicine, Section of Ophthalmology

President: Col. F. A. Juler, 96 Harley St., London, W. 1, England.
Secretary: Dr. Harold Ridley, 60 Queen Anne St., London, W. 1, England.

São Paulo Society of Ophthalmology

President: Dr. Armando Gallo, Rua Benjamin Constant, 67, 9° Andar São Paulo, Brazil.
Secretary: Dr. F. Amédée Féret Filho, Rua Marconi, 48, 4° Andar, São Paulo, Brazil.

Scottish Ophthalmological Club

President: Dr. S. Spence Meighan, 13 Woodside Pl., Glasgow, C. 3.
Secretary: Dr. Alexander Garrow, 15 Woodside Pl., Glasgow, C. 3.
Place: Edinburgh and Glasgow, in rotation.

Sociedad Argentina de Oftalmologia

Chairman: Dr. Jorge Malbrán, Buenos Aires.
Secretary: Dr. Benito Just Tiscornia, Santa Fe 1171, Buenos Aires.

Sociedad Cubana de Oftalmologia

President: Prof. Lorenzo Comas, Calle D #461, Vedado, Habana, Cuba.
Secretary: Dr. Oscar F. Horstmann, Calle 5ta. #702, Vedado, Habana, Cuba.
Time: Second Tuesday of every month.

Sociedad Oftalmologia del Litoral, Rosario (Argentina)

President: Prof. Dr. Carlos Weskamp, Laprida 1159, Rosario.
Secretary: Dr. Arturo Etchemendigaray, Villa Constitución, Santa Fé.
Place: Rosario. Time: Last Saturday of every month, April to November. All correspondence should be addressed to the President.

SOCIEDADE DE OFTALMOLOGÍA DEL NORTE

President: Dr. Alberto Cárdenas.
Secretary: Dr. Jorge Luis Castillo, Mendoza 421, Tucumán, Argentina.

SOCIEDADE DE OFTALMOLOGIA DE MINAS GERAIS

President: Prof. Hilton Rocha, Rua Rio de Janeiro 2251, Bello Horizonte, Minas Geraes, Brazil.
Secretary: Dr. Ennio Coscarelli, Rua Aimorés 1697, Bello Horizonte, Minas Geraes, Brazil.

SOCIEDADE DE OFTALMOLOGIA E OTORRINOLARINGOLOGIA DE RIO GRANDE DO SUL

President: Dr. Luiz Assumpção Osorio, Edificio Vera Cruz, Apartamento 134, Porto Alegre, Rio Grande do Sul.
Secretary: Dr. Fernando Voges Alves, Caixa Postal 928, Porto Alegre, Rio Grande do Sul.

SOCIEDADE DE OPHTHALMOLOGIA E OTO-RHINO-LARYNGOLOGIA DA BAHIA

President: Dr. Theonilo Amorim, Barra Avenida, Bahia, Brazil.
Secretary: Dr. Adroaldo de Alencar, Brazil.
All correspondence should be addressed to the President.

SOCIETÀ OFTALMOLOGICA ITALIANA

President: Prof. Dott. Giuseppe Ovio, Ophthalmological Clinic, University of Rome, Rome.
Secretary: Prof. Dott. Epimaco Leonardi, Via del Gianicolo, 1, Rome.

SOCIÉTÉ FRANÇAISE D'OPHTALMOLOGIE

Secretary: Dr. René Onfray, 6 Avenue de la Motte Picquet, Paris, 7e.

SOCIETY OF SWEDISH OPHTHALMOLOGISTS

Secretary: Dr. K. O. Granström, Södermalmstorg 4, Stockholm, Sö.

TEL AVIV OPHTHALMOLOGICAL SOCIETY

President: Dr. D. Arieh-Friedman, 96 Allenby St., Tel Aviv, Palestine.
Secretary: Dr. Sadger Max, 9 Bialik St., Tel Aviv, Palestine.

NATIONAL

AMERICAN MEDICAL ASSOCIATION, SCIENTIFIC ASSEMBLY, SECTION ON OPHTHALMOLOGY

Chairman: Dr. Derrick Vail, 55 E. Washington St., Chicago.
Secretary: Dr. R. J. Masters, 23 E. Ohio St., Indianapolis.
Place: Atlantic City. Time: June 9-13, 1947.

AMERICAN ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY, SECTION ON OPHTHALMOLOGY

President: Dr. Alan C. Woods, Johns Hopkins Hospital, Baltimore 5.
President-Elect: Dr. C. H. McCaskey, 20 N. Meridian St., Indianapolis, Ind.
Executive Secretary-Treasurer: Dr. William L. Benedict, 100–1st Ave. Bldg., Rochester, Minn.
Place: Palmer House, Chicago. Time: Oct. 12-17, 1947.

AMERICAN OPHTHALMOLOGICAL SOCIETY

President: Dr. John W. Burke, 1740 M St. W., Washington, D. C.
Secretary-Treasurer: Dr. Walter S. Atkinson, 129 Clinton St., Watertown, N. Y.

ASSOCIATION FOR RESEARCH IN OPHTHALMOLOGY, INC.

Chairman: Dr. Derrick Vail, 55 E. Washington St., Chicago.
Secretary-Treasurer: Dr. Brittain F. Payne, 17 E. 72d St., New York.
Assistant Secretary-Treasurer: Dr. Hunter Romaine, 35 E. 70th St., New York.

CANADIAN MEDICAL ASSOCIATION, SECTION ON OPHTHALMOLOGY

President: Dr. Alexander E. MacDonald, 170 St. George St., Toronto 5.
Secretary-Treasurer: Dr. L. J. Sebert, 170 St. George St., Toronto 5.

CANADIAN OPHTHALMOLOGICAL SOCIETY

President: Dr. J. A. MacMillan, 1410 Stanley St., Montreal.
Secretary-Treasurer: Dr. Kenneth B. Johnston, Suite 1, 1509 Sherbrooke St. W., Montreal.

NATIONAL SOCIETY FOR THE PREVENTION OF BLINDNESS

President: Mr. Mason H. Bigelow, 1790 Broadway, New York.
Secretary: Miss Regina E. Schneider, 1790 Broadway, New York.
Executive Director: Mrs. Eleanor Brown Merrill, 1790 Broadway, New York.
Place: New York. Time: Nov. 25-27, 1946.

SECTIONAL

ACADEMY OF MEDICINE OF NORTHERN NEW JERSEY, SECTION ON EYE, EAR, NOSE AND THROAT

President: Dr. Anthony Ambrose, 31 Lincoln Park, Newark.
Secretary: Dr. William F. Keim Jr., 15 Washington St., Newark 2.
Place: 91 Lincoln Park South, Newark. Time: 8:45 p. m., second Monday of each month, October to May.

CENTRAL ILLINOIS SOCIETY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President: Dr. Stuart Broadwell, 101½ N. 5th St., Springfield, Ill.
Secretary-Treasurer: Dr. William F. Hubble, 861-867 Citizens Bldg., Decatur, Ill.

CENTRAL WISCONSIN SOCIETY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President: Dr. P. G. Spelbring, 131 S. Barstow St., Eau Claire.
Secretary: Dr. G. L. McCormick, 650 S. Central Ave., Marshfield.

HAWAII EYE, EAR, NOSE AND THROAT SOCIETY

President: Dr. F. J. Pinkerton, 7 Young Hotel Bldg., Honolulu.
Secretary-Treasurer: Dr. L. Q. Pang, 52 S. Vineyard St., Honolulu 39.
Place: Honolulu. Time: Third Thursday of each month.

NEW ENGLAND OPHTHALMOLOGICAL SOCIETY

President: Dr. Howard F. Hill, 177 Main St., Waterville, Maine.
Secretary-Treasurer: Dr. Merrill J. King, 264 Beacon St., Boston 16.
Place: Massachusetts Eye and Ear Infirmary, 243 Charles St., Boston. Time: 8 p. m., third Tuesday of each month from November to April, inclusive.

PACIFIC COAST OTO-OPHTHALMOLOGICAL SOCIETY

President: Dr. D. H. O'Rourke, 1612 Tremont Pl., Denver.
Secretary-Treasurer: Dr. C. Allen Dickey, 450 Sutter St., San Francisco.

PUGET SOUND ACADEMY OF OPHTHALMOLOGY AND OTO-LARYNGOLOGY

President: Dr. Julius A. Weber, 640 Stimson Bldg., Seattle 1, Wash.
Secretary-Treasurer: Dr. Barton E. Peden, 301 Stimson Bldg., Seattle 1, Wash.
Place: Seattle or Tacoma, Wash. Time: Third Tuesday of each month except June, July and August.

ROCK RIVER VALLEY EYE, EAR, NOSE AND THROAT SOCIETY

President: Dr. J. Sheldon Clark, Sterling, Ill.
Secretary-Treasurer: Dr. Harry R. Warner, 321 W. State St., Rockford, Ill.
Place: Rockford, Ill., or Janesville or Beloit, Wis. Time: Third Tuesday of each month from October to April, inclusive.

SAGINAW VALLEY ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President: Dr. A. R. McKinney, 330 S. Washington St., Saginaw, Mich.
Secretary-Treasurer: Dr. Harold H. Heuser, 207 Davidson Bldg., Bay City, Mich.
Place: Saginaw or Bay City, Mich. Time: Second Tuesday of each month, except July, August and September.

SIOUX VALLEY EYE AND EAR ACADEMY

President: Dr. J. C. Decker, 515 Francis Bldg., Sioux City, Iowa.
Secretary-Treasurer: Dr. J. E. Dvorak, 408 Davidson Bldg., Sioux City, Iowa.

SOUTHERN MEDICAL ASSOCIATION, SECTION ON OPHTHALMOLOGY AND OTOLARYNGOLOGY

Chairman: Dr. Savage Zerfoss, 165–8th Ave. N., Nashville 3, Tenn.
Secretary: Dr. Alston Callahan, 908 S. 20th St., Birmingham 5, Ala.
Place: Miami, Florida. Time: Nov. 6, 1946.

SOUTHWESTERN ACADEMY OF EYE, EAR, NOSE AND THROAT

President: Dr. H. L. Brehmer, 221 W. Central Ave., Albuquerque, N. Mex.
Secretary: Dr. A. E. Cruthirds, 1011 Professional Bldg., Phoenix, Ariz.

SOUTHWESTERN MICHIGAN TRIOLOGICAL SOCIETY

President: Dr. W. M. Dodge, 716 First National Bank Bldg., Battle Creek.
Secretary-Treasurer: Dr. Kenneth Lowe, 25 W. Michigan Ave., Battle Creek.
Time: Last Thursday of September, October, November, March, April and May.

WESTERN PENNSYLVANIA EYE, EAR, NOSE AND THROAT SOCIETY

President: Dr. J. V. Foster, State College.
Secretary-Treasurer: Dr. J. McClure Tyson, Deposit National Bank Bldg., Dubois.

STATE

ARKANSAS STATE MEDICAL SOCIETY, EYE, EAR, NOSE AND THROAT SECTION

President: Dr. E. C. Moulton, 619 Garrison Ave., Fort Smith.
Secretary: Dr. K. W. Cosgrove, 7 Urquhart Bldg., Little Rock.

COLORADO OPHTHALMOLOGICAL SOCIETY

President: Dr. George H. Stine, 23 E. Pikes Peak Ave., Colorado Springs.
Secretary: Dr. J. Leonard Swigert, 320 Republic Bldg., Denver.
Place: University Club, Denver. Time: 7:30 p. m., third Saturday of each month, October to May, inclusive.

CONNECTICUT STATE MEDICAL SOCIETY, SECTION ON EYE, EAR, NOSE AND THROAT

President: Dr. Paul B. MacCready, 442 Temple St., New Haven.
Secretary-Treasurer: Dr. W. H. Turnley, 1 Atlantic St., Stamford, Conn.

EYE, EAR, NOSE AND THROAT CLUB OF GEORGIA

President: Dr. William O. Martin Jr., Doctors Bldg., Atlanta.
Secretary-Treasurer: Dr. C. K. McLaughlin, 666 Cherry St., Macon.

INDIANA ACADEMY OF OPHTHALMOLOGY AND OTO-LARYNGOLOGY

President: Dr. W. E. Stewart, 721 Wabash Ave., Terre Haute.
Secretary: Dr. Russell A. Sage, 23 E. Ohio St., Indianapolis.
Place: French Lick. Time: First Wednesday in April.

IOWA ACADEMY OF OPHTHALMOLOGY AND OTO-LARYNGOLOGY

President: Dr. C. S. O'Brien, University Hospital, Iowa City.
Secretary-Treasurer: Dr. Carl A. Noe, 120–3d Ave. S. E., Cedar Rapids.

KANSAS STATE MEDICAL SOCIETY, SECTION ON OPHTHALMOLOGY AND OTOLARYNGOLOGY

President: Dr. W. B. Granger, Emporia.
Secretary: Dr. George F. Gsell, 911 Beacon Bldg., Wichita 2.

LOUISIANA-MISSISSIPPI OPHTHALMOLOGICAL AND OTOLARYNGOLOGICAL SOCIETY

President: Dr. George S. Adkins, 121 N. President St., Jackson, Miss.
Secretary-Treasurer: Dr. Edley H. Jones, 1301 Washington St., Vicksburg, Miss.

MEDICAL SOCIETY OF THE STATE OF PENNSYLVANIA, SECTION ON EYE, EAR, NOSE AND THROAT DISEASES

Chairman: Dr. William T. Hunt Jr., 1205 Spruce St., Philadelphia 7.
Secretary: Dr. Gabriel Tucker, 250 S. 18th St., Philadelphia 3.

MICHIGAN STATE MEDICAL SOCIETY, SECTION OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

Chairman: Dr. Edmond L. Cooper, 1553 Woodward Ave., Detroit 26.
Secretary: Dr. Ralph H. Gilbert, 110 Fulton St. E., Grand Rapids.

MINNESOTA ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President: Dr. Karl C. Wold, 1051 Lowry Bldg., St. Paul 2.
Secretary: Dr. William A. Kennedy, 372 St. Peter St., St. Paul 2.
Time: Second Friday of each month from October to May.

MONTANA ACADEMY OF OTO-OPHTHALMOLOGY

President: Dr. H. Casebeer, 44 W. Park Ave., Butte.
Secretary: Dr. Fritz D. Hurd, 309 Medical Arts Bldg., Great Falls.

NEBRASKA ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President: Dr. W. Howard Morrison, 1500 Medical Arts Bldg., Omaha.
Secretary-Treasurer: Dr. John Peterson, 1307 N St., Lincoln.

NEW JERSEY STATE MEDICAL SOCIETY, SECTION ON OPHTHALMOLOGY, OTOLOGY AND RHINOLARYNGOLOGY

Chairman: Dr. C. W. Buvinger, 50 Washington St., East Orange.
Secretary: Dr. Z. Laurence Griesemer, 1145 E. Jersey St., Elizabeth.

NEW YORK STATE MEDICAL SOCIETY, EYE, EAR, NOSE AND THROAT SECTION

Chairman: Dr. Maxwell D. Ryan, 660 Madison Ave., New York 21.
Secretary: Dr. Thomas H. Johnson, 30 W. 59th St., New York.

NORTH CAROLINA EYE, EAR, NOSE AND THROAT SOCIETY

President: Dr. A. J. Ellington, 412 S. Spring St., Burlington.
Secretary: Dr. J. A. Harrill, Bowman Gray School of Medicine, Winston-Salem.
Place: Hendersonville. Time: Sept. 16-19, 1946.

NORTH DAKOTA ACADEMY OF OPHTHALMOLOGY AND OTO-LARYNGOLOGY

President: Dr. E. D. Perrin, 221–5th St., Bismarck.
Secretary-Treasurer: Dr. M. T. Lampert, Minot.

OREGON ACADEMY OF OPHTHALMOLOGY AND OTO-LARYNGOLOGY

President: Dr. Wilfred Belnap, 833 S. W. 11th Ave., Portland.
Secretary-Treasurer: Dr. C. W. Kuhn, 1020 S. W. Taylor St., Portland 5.
Place: Good Samaritan Hospital, Portland. Time: Third Tuesday of each month.

PENNSYLVANIA ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President: Dr. Thomas F. Furlong Jr., 36 Parking Plaza, Ardmore.
Secretary: Dr. Benjamin F. Souders, 143 N. 6th St., Reading.
Time: Last week in April.

RHODE ISLAND OPHTHALMOLOGICAL AND OTOLOGICAL SOCIETY

Acting President: Dr. N. Darrell Harvey, 112 Waterman St., Providence.
Secretary-Treasurer: Dr. Linley C. Happ, 124 Waterman St., Providence.
Place: Rhode Island Medical Society, Library, Providence. Time: 8:30 p. m., second Thursday in October, December, February and April.

SOUTH CAROLINA SOCIETY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President: Dr. J. H. Stokes, 125 W. Cheves St., Florence.
Secretary-Treasurer: Dr. Roderick Macdonald, 330 E. Main St., Rock Hill.
Place: Hendersonville, N. C. Time: Sept. 16-19, 1946.

TENNESSEE ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President: Dr. George Burchfield, Maryville.
Secretary-Treasurer: Dr. Sam H. Sanders, 1089 Madison Ave., Memphis.

TEXAS OPHTHALMOLOGICAL AND OTO-LARYNGOLOGICAL SOCIETY

President: Dr. F. H. Rosebrough, 603 Navarro St., San Antonio.
Secretary: Dr. M. K. McCullough, 1717 Pacific Ave., Dallas.

UTAH OPHTHALMOLOGICAL SOCIETY

President: Dr. E. B. Fairbanks, 315 Medical Arts Bldg., Salt Lake City.
Secretary-Treasurer: Dr. Dean Spear, 516 Boston Bldg., Salt Lake City.
Place: University Club, Salt Lake City. Time: 7:00 p. m., third Monday of each month.

VIRGINIA SOCIETY OF OTO-LARYNGOLOGY AND OPHTHALMOLOGY

President: Dr. Thomas E. Hughes, 1000 W. Grace St., Richmond.
Secretary-Treasurer: Dr. Francis H. McGovern, 105 S. Union St., Danville.

WEST VIRGINIA STATE MEDICAL ASSOCIATION, EYE, EAR, NOSE AND THROAT SECTION

President: Dr. George Traugh, 309 Cleveland Ave., Fairmont.
Secretary: Dr. Welch England, 621½ Market St., Parkersburg.

LOCAL

AKRON ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President: Dr. E. L. Mather, 39 S. Main St., Akron, Ohio.
Secretary-Treasurer: Dr. V. C. Malloy, 2d National Bank Bldg., Akron, Ohio.
Time: First Monday in January, March, May and November.

Atlanta Eye, Ear, Nose and Throat Society

President: Dr. B. M. Cline, 153 Peachtree St. N. E., Atlanta, Ga.
Secretary: Dr. Lester A. Brown, 815 Doctors Bldg., Atlanta, Ga.
Place: Academy of Medicine. Time: 7:30 p. m., fourth Monday of each month from October to May.

Baltimore Medical Society, Section on Ophthalmology

Chairman: Dr. Jonas Friedenwald, 1212 Eutaw Pl., Baltimore.
Secretary: Dr. Fred Reese, 330 N. Charles St., Baltimore 1.
Place: Medical and Chirurgical Faculty, 1211 Cathedral St. Time: 8:30 p. m., fourth Thursday of each month from October to March.

Birmingham Eye, Ear, Nose and Throat Club

President: Each member, in alphabetical order.
Secretary: Dr. W. Chunn Parsons, 425 Woodward Bldg., Birmingham, Ala.
Place: Tutwiler Hotel. Time: 6:30 p. m., second Tuesday of each month, September to May, inclusive.

Brooklyn Ophthalmological Society

President: Dr. Benjamin C. Rosenthal, 140 New York Ave., Brooklyn.
Secretary-Treasurer: Dr. Louis Freimark, 256 Rochester Ave., Brooklyn 13.
Place: Kings County Medical Society Bldg., 1313 Bedford Ave. Time: Third Thursday in February, April, May, October and December.

Buffalo Ophthalmologic Club

President: Dr. William M. Howard, 389 Linwood Ave., Buffalo 9.
Secretary-Treasurer: Dr. Sheldon B. Freeman, 196 Linwood Ave., Buffalo 9.
Time: Second Thursday of each month from October to May.

Chattanooga Society of Ophthalmology and Otolaryngology

President: Each member, in alphabetical order.
Secretary: Dr. Douglas Chamberlain, Providence Bldg., Chattanooga, Tenn.
Place: Mountain City Club. Time: Second Thursday of each month from September to May.

Chicago Ophthalmological Society

President: Dr. W. A. Mann, 30 N. Michigan Ave., Chicago 2.
Secretary: Dr. J. R. Fitzgerald, 3215 W. North Ave., Chicago.
Place: Continental Hotel, 505 N. Michigan Ave. Time: Third Monday of each month from October to May.

Cincinnati General Hospital Ophthalmology Staff

Chairman: Dr. D. T. Vail, 441 Vine St., Cincinnati.
Secretary: Dr. A. A. Levin, 441 Vine St., Cincinnati.
Place: Cincinnati General Hospital. Time: 7:45 p. m., third Friday of each month except June, July and August.

Cleveland Ophthalmological Club

Chairman: Dr. M. Paul Motto, Rose Bldg., Cleveland.
Secretary: Dr. H. H. Wygand, 624 Guardian Bldg., Cleveland.
Time: Second Tuesday in October, December, February and April.

College of Physicians, Philadelphia, Section on Ophthalmology

Chairman: Dr. Burton Chance, 317 S. 15th St., Philadelphia.
Clerk: Dr. George F. J. Kelly, 37 S. 20th St., Philadelphia.
Time: Third Thursday of every month from October to April, inclusive.

Columbus Ophthalmological and Oto-Laryngological Society

Chairman: Dr. M. Goldberg, 328 E. State St., Columbus, Ohio.
Secretary-Treasurer: Dr. W. J. Miller, 21 E. State St., Columbus, Ohio.
Place: University Club. Time: 6:15 p. m., first Monday of each month, from October to May, inclusive.

Corpus Christi Eye, Ear, Nose and Throat Society

Chairman: Dr. L. W. O. Janssen, 710 Medical Professional Bldg., Corpus Christi, Texas.
Secretary: Dr. F. B. Kelly, 519 Medical Professional Bldg., Corpus Christi, Texas.
Time: 6:30 p. m., third Tuesday of each month from October to May.

Dallas Academy of Ophthalmology and Oto-Laryngology

President: Dr. Speight Jenkins, 1719 Pacific Ave., Dallas, Texas.
Secretary: Dr. L. Darrough, Dallas Medical and Surgical Clinics, Dallas, Texas.
Place: Dallas Athletic Club. Time: 6:30 p. m., first Tuesday of each month from October to June. The November, January and March meetings are devoted to clinical work.

Des Moines Academy of Ophthalmology and Otolaryngology

President: Dr. H. I. McPherrin, 406–6th Ave., Des Moines, Iowa.
Secretary-Treasurer: Dr. C. C. Jones, Bankers Trust Bldg., Des Moines, Iowa.
Time: 7:45 p. m., fourth Monday of every month from September to May.

Detroit Ophthalmological Club

Chairman: Members rotate alphabetically.
Secretary: Dr. Wesley G. Reid, 974 Fisher Bldg., Detroit 2.
Place: Club rooms of Wayne County Medical Society. Time: First Monday of each month, November to April, inclusive.

Detroit Ophthalmological Society

President: Dr. Bruce Fralick, 201 S. Main St., Ann Arbor, Mich.
Secretary: Dr. William S. Gonne, 619 David Whitney Bldg., Detroit 26.
Place: Club rooms of Wayne County Medical Society. Time: 6:30 p. m., third Thursday of each month from November to April, inclusive.

Eastern New York Eye, Ear, Nose and Throat Association

President: Dr. Frank C. Furlong, 713 Union St., Schenectady.
Secretary-Treasurer: Dr. E. Martin Freund, 762 Madison Ave., Albany.
Time: Third Wednesday in October, November, March, April, May and June.

Fort Worth Eye, Ear, Nose and Throat Society

President: Dr. C. R. Lees, 602 W. 10th St., Fort Worth 2, Texas.
Secretary-Treasurer: Dr. Van D. Rathgeber, 1305 Medical Arts Bldg., Fort Worth, Texas.
Place: Medical Hall, Medical Arts Bldg. Time: 7:30 p. m., first Friday of each month except July and August.

Houston Academy of Medicine, Ophthalmological and Oto-Laryngological Section

President: Dr. J. Matt Robison, 1304 Walker Ave., Houston, Texas.
Secretary: Dr. John H. Barrett, 1304 Walker Ave., Houston, Texas.
Place: River Oaks Country Club. Time: 6:30 p. m., second Thursday of each month from October to June.

INDIANAPOLIS OPHTHALMOLOGICAL AND OTOLARYNGOLOGICAL SOCIETY

President: Dr. J. Jerome Littell, 603 Hume Mansur Bldg., Indianapolis.
Secretary: Dr. J. Lawrence Sims, 23 E. Ohio St., Indianapolis.
Place: Indianapolis Athletic Club. Time: 6:30 p. m., second Thursday of each month from November to May.

KANSAS CITY SOCIETY OF OPHTHALMOLOGY AND OTO-LARYNGOLOGY

President: Dr. Edgar Johnson, 906 Grand Ave., Kansas City, Mo.
Secretary: Dr. W. E. Keith, 1103 Grand Ave., Kansas City, Mo.
Time: Third Thursday of each month from October to June. The November, January and March meetings are devoted to clinical work.

LONG BEACH EYE, EAR, NOSE AND THROAT SOCIETY

Chairman: Dr. Robert G. Thornburgh, 117 E. 8th St., Long Beach 2, Calif.
Secretary-Treasurer: Dr. Kirt Parks, 605 Professional Bldg., Long Beach 2, Calif.
Place: Seaside Hospital. Time: Last Wednesday of each month from October to May.

LOS ANGELES SOCIETY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President: Dr. A. R. Robbins, 1930 Wilshire Blvd., Los Angeles.
Secretary-Treasurer: Dr. K. C. Brandenburg, 110 Pine Ave., Long Beach 2, Calif.
Place: Los Angeles County Medical Association Bldg., 1925 Wilshire Blvd. Time: 6:30 p. m., fourth Monday of each month from September to May, inclusive.

LOUISVILLE EYE AND EAR SOCIETY

President: Dr. Joseph S. Heitger, Heyburn Bldg., Louisville, Ky.
Secretary-Treasurer: Dr. J. W. Fish, 321 W. Broadway, Louisville, Ky.
Place: Brown Hotel. Time: 6:30 p. m., second Thursday of each month from September to May, inclusive.

LOWER ANTHRACITE EYE, EAR, NOSE AND THROAT SOCIETY

Chairman: Each member in alphabetical order.
Secretary: Dr. James J. Monohan, 31 S. Jardin St., Shenandoah, Pa.

MEDICAL SOCIETY OF THE DISTRICT OF COLUMBIA, SECTION OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

Chairman: Dr. P. S. Constantinople, 1835 I St. N. W., Washington.
Secretary: Dr. Frazier Williams, 1801 I St. N. W., Washington.
Place: 1718 M St. N. W. Time: 8 p. m., third Friday of each month from October to April, inclusive.

MEMPHIS SOCIETY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

Chairman: Each member, in alphabetical order.
Secretary: Dr. Sam H. Sanders, 1089 Madison Ave., Memphis, Tenn.
Place: Eye Clinic of Memphis Eye, Ear, Nose and Throat Hospital. Time: 8 p. m., second Tuesday of each month from September to May.

MILWAUKEE OTO-OPHTHALMIC SOCIETY

President: Dr. Ralph T. Rank, 238 W. Wisconsin Ave., Milwaukee.
Secretary-Treasurer: Dr. Frank G. Treskow, 411 E. Mason St., Milwaukee 2.
Place: University Club. Time: 6:30 p. m., fourth Tuesday of each month from October to May.

MONTGOMERY COUNTY MEDICAL SOCIETY

Chairman: Dr. H. V. Dutrow, 1040 Fidelity Medical Bldg., Dayton, Ohio.
Secretary-Treasurer: Dr. Maitland D. Place, 981 Reibold Bldg., Dayton, Ohio.
Place: Van Cleve Hotel. Time: 6:30 p. m., first Tuesday of each month from October to June, inclusive.

Montreal Ophthalmological Society

President: Dr. L. F. Badeaux, 502 Cherrier St., Montreal, Canada.
Secretary: Dr. John V. V. Nicholls, 1414 Drummond St., Montreal, Canada.
Time: Second Thursday of October, December, February and April.

Nashville Academy of Ophthalmology and Otolaryngology

Chairman: Dr. M. M. Cullom, 700 Church St., Nashville, Tenn.
Secretary: Dr. R. E. Sullivan, 432 Doctors Bldg., Nashville 3, Tenn.
Place: James Robertson Hotel. Time: 6:30 p. m., third Monday of each month from October to May.

New Orleans Ophthalmological and Otolaryngological Society

President Dr. W. B. Clark, 1012 American Bank Bldg., New Orleans.
Secretary: Dr. Mercer G. Lynch, 1018 Maison Blanche Bldg., New Orleans.
Place: Louisiana State University Medical Bldg. Time: 8 p. m., second Tuesday of each month from October to May.

New York Academy of Medicine, Section of Ophthalmology

Chairman: Dr. Brittain F. Payne, 17 E. 72d St., New York 21.
Secretary: Dr. Milton Berliner, 57 W. 57th St., New York.
Time: 8:30 p. m., third Monday of every month from October to May, inclusive.

New York Society for Clinical Ophthalmology

President: Dr. Benjamin Friedman, 6 W. 77th St., New York.
Secretary: Dr. Benjamin Esterman, 983 Park Ave., New York 28.
Place: New York Academy of Medicine, 2 E. 103d St. Time: 8 p. m., first Monday of each month from October to May, inclusive.

Oklahoma City Academy of Ophthalmology and Otolaryngology

President: Dr. S. R. Shaver, 117 N. Broadway, Oklahoma City.
Secretary: Dr. William Mussil, Medical Arts Bldg., Oklahoma City.
Place: University Hospital. Time: Second Tuesday of each month from September to May.

Omaha and Council Bluffs Ophthalmological and Oto-Laryngological Society

President: Dr. A. A. Steinberg, 1502 Farnam St., Omaha.
Secretary-Treasurer: Dr. W. Howard Morrison, 1500 Medical Arts Bldg., Omaha 2.
Place: Omaha Club, 20th and Douglas Sts., Omaha. Time: 6 p. m. dinner; 7 p. m. program; third Wednesday of each month from October to May.

Passaic-Bergen Ophthalmological Club

President: Dr. Thomas Sanfacon, 340 Park Ave., Paterson, N. J.
Secretary-Treasurer: Dr. J. Averbach, 435 Clifton Ave., Clifton, N. J.
Place: Paterson Eye and Ear Infirmary. Time: 9 p. m., last Friday of every month, except June, July and August.

Philadelphia County Medical Society, Eye Section

President: Dr. L. Waller Winckler, Philadelphia.
Secretary: Dr. Robert T. M. Donnelly, 255 S. 17th St., Philadelphia.
Time: First Thursday of each month from October to May.

Pittsburgh Ophthalmological Society

President: Dr. Jay G. Linn, Jenkins Arcade, Pittsburgh.
Secretary: Dr. Robert J. Billings, Jenkins Arcade, Pittsburgh.
Place: Pittsburgh Academy of Medicine Bldg. Time: Fourth Monday of each month, except June, July, August and September.

READING EYE, EAR, NOSE AND THROAT SOCIETY

President: Dr. Claude W. Bankes, 212 N. 6th St., Reading, Pa.
Secretary: Dr. Paul C. Craig, 232 N. 5th St., Reading, Pa.
Place: Wyomissing Club. Time: 6:30 p. m., third Wednesday of each month from September to July.

RICHMOND EYE, EAR, NOSE AND THROAT SOCIETY

President: Dr. Luther C. Brawner, Professional Bldg., Richmond, Va.
Secretary: Dr. Clifford A. Folkes, Professional Bldg., Richmond, Va.
Place: Westmoreland Club. Time: 6 p. m., second Monday of each month from October to May.

ROCHESTER EYE, EAR, NOSE AND THROAT SOCIETY

President: Dr. Frank Barber, 75 S. Fitzhugh St., Rochester, N. Y.
Secretary-Treasurer: Dr. Charles T. Sullivan, 277 Alexander St., Rochester, N. Y.

ST. LOUIS OPHTHALMIC SOCIETY

President: Dr. A. Lange, 3903a Olive St., St. Louis.
Secretary: Dr. William Kleinberg, Frisco Bldg., St. Louis.
Place: Oscar Johnson Institute. Time: Fourth Friday of each month from October to April, inclusive, except December, at 8:00 p. m.

SAN ANTONIO OPHTHALMO-OTO-LARYNGOLOGICAL SOCIETY

President: Dr. James P. Aderhold, Medical Arts Bldg., San Antonio, Texas.
Secretary-Treasurer: Dr. Virgil S. Steele, South Texas Bldg., San Antonio, Texas.
Place: San Antonio Texas, and Brooke General Hospital. Time: 7 p. m., second Tuesday of each month from September to May.

SAN FRANCISCO COUNTY MEDICAL SOCIETY, SECTION ON EYE, EAR, NOSE AND THROAT

Chairman: Dr. C. B. Cowan, 490 Post St., San Francisco.
Secretary: Dr. D. Harrington, 384 Post St., San Francisco.
Place: Society's Bldg., 2180 Washington St., San Francisco. Time: Fourth Tuesday of every month except June, July and December.

SHREVEPORT EYE, EAR, NOSE AND THROAT SOCIETY

President: Dr. David C. Swearingen, Slattery Bldg., Shreveport, La.
Secretary-Treasurer: Dr. Kenneth Jones, Medical Arts Bldg., Shreveport, La.
Place: Shreveport Charity Hospital. Time: 7:30 p. m., first Monday of every month except July, August and September.

SPOKANE ACADEMY OF OPHTHALMOLOGY AND OTO-LARYNGOLOGY

President: Dr. Robert L. Pohl, W. 1104, 21st Ave., Spokane, Wash.
Secretary: Dr. Malcolm N. Wilmes, 407 Riverside Ave., Spokane, Wash.
Place: Spokane Medical Library. Time: 8 p. m., fourth Tuesday of each month except June, July and August.

SYRACUSE EYE, EAR, NOSE AND THROAT SOCIETY

President: Dr. A. H. Rubenstein, 713 E. Genesee St., Syracuse, N. Y.
Secretary-Treasurer: Dr. I. H. Blaisdell, 713 E. Genesee St., Syracuse, N. Y.
Place: University Club. Time: First Tuesday of each month except June, July and August.

TOLEDO EYE, EAR, NOSE AND THROAT SOCIETY

Chairman: Dr. W. W. Randolph, 1838 Parkwood Ave., Toledo 2, Ohio.
Secretary: Dr. John L. Roberts, 316 Michigan St., Toledo, Ohio.
Place: Toledo Club. Time: Each month except June, July and August.

TORONTO ACADEMY OF MEDICINE, SECTION OF OPHTHALMOLOGY

Chairman: Dr. R. G. C. Kelly, 14 Lynwood Ave., Toronto 5, Canada.
Secretary: Dr. Alfred J. Elliot, 802 Medical Arts Bldg., Toronto 5, Canada.
Place: Academy of Medicine, 13 Queens Park. Time: First Monday of each month, November to April.

WASHINGTON, D. C., OPHTHALMOLOGICAL SOCIETY

President: Dr. Harold M. Downey, 1740 M St. N. W., Washington, D. C.
Secretary-Treasurer: Dr. Richard W. Wilkinson, 1408 L St. N. W., Washington, D. C.
Place: Medical Society of District of Columbia Bldg., 1718 M St. N. W., Washington, D. C. Time: 7:30 p. m., first Monday in November, January, March and May.

WILKES-BARRE OPHTHALMOLOGICAL SOCIETY

Chairman: Each member in turn.
Secretary: Dr. Samuel T. Buckman, 70 S. Franklin St., Wilkes-Barre, Pa.
Place: Office of chairman. Time: Last Tuesday of each month from October to May.